Physical Activity and Breast Cancer

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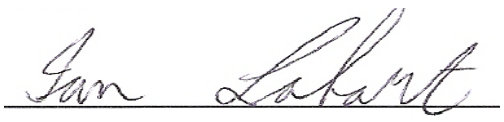
Signature 

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ABSTRACT

Background: Breast cancer is the most frequently diagnosed cancer and a leading cause of cancer death among females, both worldwide and in the UK. Although, UK incidence of breast cancer is rising, breast cancer mortality rates are falling, due largely to early detection and improved treatment. As a result there are more women living with a diagnosis of breast cancer than ever before. Due mainly to side-effects of adjuvant therapy, breast cancer patients may require diagnostic, therapeutic, supportive or palliative services many years post-diagnosis, which poses a major challenge to already stretched healthcare services. Accordingly, effective and inexpensive interventions that can alleviate treatment side-effects, improve health, quality of life and potentially reduce risk of early mortality are required for breast cancer patients. Awareness of the positive influence that physical activity can have on breast cancer development and outcome is an important determinant of physical activity levels. A higher level of physical activity before and after breast cancer diagnosis is related to a lower risk of all-cause and breast cancer-related mortality. Randomised controlled trials have reported beneficial effects of physical activity interventions on outcomes relating to health, quality of life and mortality risk among breast cancer survivors.

Aims: The present project aimed to: 1) assess awareness of the role of physical activity on breast cancer risk and the sufficiency of physical activity undertaken in women attending the NHS breast screening programme (NHSBSP), 2) compare physical activity levels of women at different stages of breast cancer pathway, 3) investigate the effects of a low-cost six-month home-based physical activity intervention on physical activity, body mass, health-related quality of life (HRQoL), insulin resistance and blood lipid profiles of breast cancer survivors and 4) assess the effects of our home-based intervention on cardiorespiratory fitness in a subset of breast cancer survivors.

Methods: A total of 309 volunteers (188 NHSBSP attendees, 41 breast cancer patients undergoing chemotherapy and 80 post-treatment breast cancer survivors) participated in the current project. Physical activity was assessed via the International Physical activity Questionnaires (IPAQ). In studies one and two, Body mass and body mass index (BMI) were assessed directly in chemotherapy patients and breast cancer survivors, and indirectly from self-reported values in NHSBSP attendees. While in study three, body fat percentage was measured via bioelectrical impedance analysis, HRQoL was assessed using the Functional

Assessment of Cancer Therapy-Breast (FACT-B) questionnaire and fasting blood samples were taken to measure lipid, glucose and insulin concentrations at baseline and post-six month home-based physical activity intervention. In study four, a random subsample of 32 breast cancer survivors undertook an exercise tolerance test to establish peak oxygen uptake values.

Results: A high proportion (70%) of NHSBSP attendees engaged in low-moderate levels of physical activity and performed low amounts of recreational physical activity. Attendees demonstrated high awareness (75%) of the role of physical activity in reducing breast cancer risk but those categorised as “low activity” were significantly unaware of insufficiency of activity ($p<0.05$). Chemotherapy patients and breast cancer survivors had significantly lower levels of total physical activity than NHSBSP attendees ($p<0.001$ and $p<0.05$, respectively). The randomised controlled trial revealed significant improvements in total physical activity, body mass ($p<0.05$), BMI ($p<0.05$) HRQoL (breast cancer subscale, $p<0.01$; trial outcome index, $p<0.05$) and total ($p<0.01$) and low-density lipoprotein ($p<0.05$) cholesterol concentrations in the intervention group compared to usual care, and significant improvements in cardiorespiratory fitness ($p<0.05$) in a subsample of breast cancer survivors allocated to intervention.

Conclusions: Physical activity interventions that incorporate strategies aimed at increasing awareness of recommended physical activity guidelines may be required in populations at risk of breast cancer. A relatively large proportion of women at risk of breast cancer may not be sufficiently exposed to the potential benefits of physical activity on breast cancer outcomes. Post-treatment breast cancer patients may be more receptive to physical activity interventions as the negative effects of chemotherapy begin to resolve, and therefore, may benefit from physical activity interventions. Results suggest that a low-cost home-based physical activity intervention with counselling and telephone support can improve the health and HRQoL of breast cancer survivors, which may in turn potentially reduce risk of breast cancer and cardiovascular disease-related mortality. Given the encouraging results and its highly portable and feasible nature, our intervention represents a promising tool for use in health and community settings to benefit large numbers of breast cancer survivors. The current project supports the inclusion of physical activity promotion as an integral component for the management and care of breast cancer survivors.

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AWKNOWLEDGEMENTS

The present thesis is dedicated to my wife, Yupa, who has given me love, support and encouragement throughout this occasionally arduous process. Along with Yupa, my stepdaughter, Ruby, and sons, Oisín and Tadhg, allowed me a broader perspective, provided a constant source of inspiration, kept me motivated and gave me strength to overcome difficulties along the way. My gratitude also to my mother for showing me the importance of hard work, and sister, Marie, and brother, Edward, for their support along the way. I am also grateful to the Deegan aunts, uncles and cousins who have made such an impact on how I think and view the world.

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This thesis is in memory of my cousin, Jason, beloved and missed by all those he has left behind.

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LIST OF PUBLICATIONS

Lahart IM, Reich C, Metsios GS, Nevill AM, Carmichael AR. Physical activity and awareness in breast screening attendees in Black Country, UK (in press). *Health Promotion International*.

Lahart IM, Metsios GS, Nevill AM, Carmichael AR. (2014) Physical activity levels in women attending breast screening, receiving chemotherapy and post-breast cancer treatment; a cross-sectional study. *International Journal of Environmental Research and Public Health*. May 20; 11(5):5487-96.

Conference presentations

Lahart IM, Metsios GS, Carmichael AR. and Nevill AM. Effects of a home-based physical activity intervention on body mass, physical activity and health-related quality of life in breast cancer patients. *British Association of Sport and Exercise Sciences Conference*; University of Essex, Essex, UK. 06-08th September 2011.

Lahart, I. Reichl, C., Metsios, G., Carmichael, A. Physical activity, body mass index, and awareness of breast cancer risk factors in women attending National Health Service Breast Screening Programme in the UK. *International Convention on Science, Education & Medicine in Sport*; Glasgow, UK. 19-24th July 2012.

CHAPTER ONE: INTRODUCTION

Breast cancer affects both men and women; however, the incidence is much higher for women. Overall, women are at 100-fold higher risk of breast cancer than men (Thomas, 1993). Therefore, female breast cancer will be the focus of this thesis. Worldwide, female breast cancer is the most frequently diagnosed cancer and a leading cause of cancer death among females, accounting for 23% of total cancer cases and 14% of cancer deaths in 2008 (Jemal et al., 2011). In the UK, it has the highest incidence (i.e. number of new cases per year) of all cancers and is second only to lung cancer as the highest cause of cancer-related mortality (ONS, 2012).

Breast cancer results from a single transformed cell that proliferates at an unregulated rate and multiplies to form a growth of abnormal cells (tumour) within the breast tissue. The transformation of a normal breast cell into a cancerous one is initiated by a genetic mutation in a somatic (any cell other than gamete or sex cells) breast cell or breast stem cell through exposure to appropriate doses of a carcinogenic agent (Porth, 2011). The cancer cell and its subsequent generations of daughter cells acquire further mutations during cell division conferring a number of capabilities upon the cancer cells, such as sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, reprogramming of energy metabolism, evading immune destruction, and activating invasion and potentially spreading to distant parts of the body (i.e. metastasis) (Hanahan and Weinberg, 2011).

While the exact cause of the genetic mutations that induce breast cancer is unknown, there are a number of risk factors associated with an increased risk of breast cancer (see sections 2.4 and 2.5). The strongest risk factors for the

development of a first primary invasive breast cancer are older age, previous history of breast lesions, a family history of breast cancer (particularly in a first-degree relative), inheritance of a genetic mutation, such as the Breast Cancer genes (BRCA) 1 and 2, and very high breast density (NBOCC, 2009; Weir et al., 2007; Ellis et al., 2003). Other risk factors that confer a moderate to modest increase in risk of breast cancer include living in a 'developed' more-affluent country, menstrual and reproductive factors, exposure to endogenous (coming from within the body) and exogenous (coming from outside the body) hormones, dietary fat and alcohol intake, height, being overweight or obese, inactivity and increased sedentary behaviour (NBOCC, 2009; Weir et al., 2007).

Because some of these risk factors are either non-modifiable or difficult to modify, researchers have focused on inducing change in modifiable risk factors. Alcohol intake, overweight/obesity and inactivity/sedentary behaviour are perhaps the most modifiable risk factors associated with breast cancer. Investigating and reducing inactivity or sedentary behavior (i.e. increased physical activity) in breast cancer populations will be the focus of this thesis. There is evidence that physical activity can reduce the risk of breast cancer either dependent or independent of reducing adiposity (body fat) (Lynch et al., 2010; Neilson et al., 2009). In the most recent epidemiological review, physical activity participation of two to three hours per week was associated with an average breast cancer risk reduction of 9%, and a 30% risk reduction with 6.5 hours of weekly physical activity (Lynch et al., 2010). The mechanism for this beneficial role of physical activity on breast cancer risk has been attributed to a number of factors, including decreased adiposity, reduced exposure to oestrogen and androgens, lower conversion of androgens to oestrogens, increased insulin sensitivity and positive influence on inflammatory cytokines (Neilson et al., 2009; Key et al., 2002).

In 2008, only 29% of women aged 16 and over were meeting the current recommended physical activity guidelines, that is achieving at least 150 minutes of moderate intensity activity in bouts of 10 minutes or more over a week, 75 minutes of vigorous intensity activity spread across a week, or a combination of moderate and vigorous intensity activity throughout a week (Bull and the Expert Working Groups, 2010; Roth, 2009). Based on these data, many women are not sufficiently active to avail of the potential breast cancer risk-reducing benefits of physical activity. However, relevant data from a UK based population at risk of breast cancer are lacking. Therefore, the aims of the first study presented in this thesis (section 5.1) was to explore, primarily, the physical activity and secondarily, overweight/obesity prevalence of a cross-section of women attending National Health Service breast screening (NHSBSP), and to examine the awareness levels of these women regarding the sufficiency of their physical activity levels and the potential breast cancer risk influence associated with physical activity and postmenopausal overweight/obesity.

Due to the increasingly early diagnosis of breast cancer and improvements in breast cancer treatment, more women are living longer after diagnosis (Ferlay et al., 2010). However, the risk of recurrence and development of a second primary breast cancer is a continued source of anxiety for breast cancer survivors (i.e. patients diagnosed with operable breast cancer who have completed all adjuvant therapy apart from hormone therapy). Epidemiological evidence suggests that breast cancer survivors who perform the highest amounts of physical activity compared to inactive or minimally active breast cancer survivors have a lower risk of breast cancer recurrence and improved overall survival (Beasley et al., 2012; Ibrahim and Al-Homaidh, 2011) (section 2.8). The mechanisms for this beneficial effect on breast cancer progression and mortality appear to be similar to those

attributed to breast cancer prevention, such as reduced adiposity, lower exposure to both oestrogens and androgens and positive influences on insulin-related factors and inflammatory biomarkers.

However, research in the USA has found that physical activity levels are generally low among breast cancer survivors with many women decreasing their physical activity following diagnosis (Irwin et al., 2003; Irwin et al., 2004). It is unknown whether this is also true in UK breast cancer populations. Therefore, we adopted a cross-sectional approach to assess whether physical activity levels of breast cancer patients undergoing systemic therapy and breast cancer patients post-systemic therapy (baseline data from participants in study's 3 and 4) were different from those of women not diagnosed with breast cancer (for this the breast screening attendees investigated in study 1 were used) (section 5.2).

Breast cancer treatment and in particular the use of adjuvant systemic treatment, such as chemotherapy and biologic and hormone therapy, can result in significant short- and long-term side effects (section 2.7). Short-term effects such as nausea, emesis (vomiting), alopecia (hair loss), myelosuppression (suppression of the bone marrow's production of blood cells and platelets), stomatitis (oral inflammation), thromboembolism (blocking of a blood vessel by a particle that has broken away from a blood clot), myalgia (pain in one or more muscles), neuropathy (abnormal and usually degenerative state of the nervous system or nerves), cognitive dysfunction, fatigue, sore eyes, difficulty sleeping and changes in sexual functioning have a significant detrimental impact on breast cancer patients' health-related quality of life (HRQoL) (Mishra et al., 2012; Kayl and Meyers, 2006; Partridge et al., 2001; Sitzia and Huggins, 1998).

Long-term effects of adjuvant systemic therapy include cardiotoxicity, neurotoxicity, secondary leukemia, lymphedema, premature menopause, sexual dysfunction, infertility, weight gain and fatigue (Azim et al., 2011; Bovelli et al., 2010). Particularly worrisome is the cardiotoxicity associated with some forms of systemic therapy, which can reduce survival rates in breast cancer patients so that the benefits derived by chemotherapy are negated.

Physical activity interventions have been investigated in randomized controlled trials (RCTs) as a possible strategy to alleviate some of both the short and long-term side effects of cancer therapy and improve overall HRQoL and psychological well-being in breast cancer survivors (Mishra et al., 2012; Speck et al., 2011; McNeeley et al., 2006). These studies have reported potential benefits of physical activity interventions in the management and/or rehabilitation of breast cancer patients post-treatment including the preservation or restoration cardiorespiratory function, muscle and bone strength and mobility, all of which can be adversely affected by cancer therapy (Speck et al., 2011).

However, most physical activity intervention trials consist of either entirely or partly facility-based supervised interventions, and therefore, the findings of these trials have limited generalisability to patients who have limited access to exercise facilities because of transportation or time-related difficulties. Home-based interventions may be advantageous as they provide a low-cost to alternative supervised, facility-based interventions that mitigate most of the transport and time-related difficulties. Therefore, a low-cost home-based physical activity intervention for breast cancer survivors within 12-months of completion of all adjuvant therapy except hormone therapy was developed (section 5.3, study 3). Study three adopted a RCT design to compare the effects of six-month home-

based physical activity intervention on primarily the physical activity levels of breast cancer survivors to usual care. Secondary outcomes included anthropometric measures, HRQoL and concentrations of blood biomarkers, such as blood lipid concentrations and insulin resistance of breast cancer survivors. The effects of the home-based intervention on cardiorespiratory fitness compared to usual care were assessed in a sub-sample of patients in study four (section 5.4).

Chapter two consists of a comprehensive description of the classification and diagnosis of breast cancer, and a presentation of the current knowledge on the aetiology, pathogenesis of the disease, risk factors for both familial (inherited) and sporadic (non-inherited) breast cancer and the treatment and side effects associated with breast cancer therapy. In addition, section 2.7 includes a review of the epidemiological research investigating the association between physical activity and mortality and recurrence in breast cancer survivors and is followed by a systematic review of trials of physical activity interventions in breast cancer survivors in section 2.8. The aims and objectives and hypotheses of this current thesis are provided in chapter three, while the methods and findings of the studies are presented in chapters four and five, respectively. Finally, the applications, limitations and future recommendations for practice and research are discussed in chapters six, seven and eight.

CHAPTER TWO: LITERATURE REVIEW

The following chapter includes an overview of the definition, diagnosis and classifications of breast cancer. Subsequently, breast cancer prevalence, incidence, mortality and survival statistics are outlined in section 2.2. The next section (2.3) describes the possible causes of breast cancer and reviews the progression of breast cancer from malignancy to metastasis. Section 2.4 and 2.5 provides a summary of the genetic risk factors for familial breast cancer and risk factors of sporadic breast cancer, respectively. In particular, the role of endogenous hormone exposure, overweight/obesity and physical activity on the effects of breast cancer risk is reviewed. A summary of the treatment and side-effects associated with breast cancer therapy is included in section 2.6. Finally, sections 2.7 and 2.8 comprise of systematic reviews and meta-analyses of the effect of physical activity on breast cancer outcomes in breast cancer survivors and the effect of physical activity interventions for breast cancer survivors, respectively.

2.1 Definition, diagnosis and classification of breast cancer

2.1.1 Definition of breast cancer

Cancer is a generic term that encompasses a group of more than two hundred diseases sharing common characteristics (Gabriel, 2007). Cancer develops when somatic cells acquire mutations which enable them to overcome numerous intrinsic and extrinsic barriers allowing them to replicate uncontrollably and spread to other parts of the body (Pelengaris and Khan, 2013). Normal cell renewal and repair involves two distinct processes: a) cell proliferation, which is the process of cell division, and b) cell differentiation, which is the process of specialization whereby new cells acquire the structural, microscopic and functional characteristics of the cells they replace (Porth, 2011). Tumour and neoplasm

(meaning “new growth”) are interchangeable terms used to describe a diverse group of conditions associated with uncontrolled cell proliferation. If a tumour is confined locally, composed of well-differentiated cells that resemble the structure and function of normal original cells but has lost its ability to control proliferation, it is described as a benign or non-cancerous tumour. However, if uncontrolled cell proliferation is accompanied by a loss of control of differentiation and invasion of surrounding tissues or spread to distant sites (metastasis) then the resulting neoplasm is described as a malignant or cancerous tumour (Pelengaris and Khan, 2013).

In malignant tumours, the accumulation of neoplastic cells may result from not only uncontrolled cell proliferation but also from evasion of apoptosis (programmed cell death that eliminates senescent and damaged or unwanted cells and deoxyribonucleic acid, DNA) (Gabriel, 2007). Both benign and malignant tumours consist of parenchymal tissue, which is composed of the neoplastic cells, and supporting non-neoplastic stromal tissue, which comprises of connective tissue, extracellular matrix and blood vessels (Porth, 2011). Tumours can be liquid, as in the cases of leukaemia and lymphomas, which comprise of neoplastic cells whose precursors are usually mobile, or they can be solid, as in the case of cancers such as breast cancer, which arise from the epithelial cells and are usually immobile (Vogelstein and Kinzler, 2004).

Pathologically, cancers are defined based on their site of origin. Carcinomas are cancers which originate from the epithelial cells in the skin or tissues lining or covering internal organs (~70% of cancer cases), sarcomas begin in bone, cartilage, fat, muscle, blood vessels or other connective/supportive tissue, leukaemia forms in blood-forming tissues such as the bone marrow and causes

the production of abnormal blood cells, while lymphomas arise in the cells of the immune system (Pelengaris and Khan, 2013). Most breast cancers are carcinomas. Although rare, sarcoma's can develop in the stromal tissues (i.e. connective tissues including muscle, fat and blood vessels) within the breast (e.g. phyllodes tumour) (Esteva and Gutierrez, 2010).

Breast carcinomas are typically sub-divided into two major categories, *in situ* disease or invasive cancer. *In situ* disease describes tumours which remain either in the ducts (tubes which carry breast milk from the lobes to the nipple), referred to as ductal carcinoma *in situ* (DCIS), and those which remain in the lobules (milk producing part of breast), known as lobular carcinoma *in situ* (LCIS) (Gabriel, 2007) (see figure 2.1. for anatomy of breast). Although most research uses the term DCIS to describe proliferative lesions within the ducts of the breasts, DCIS is actually one of four categories, which are collectively defined as intraductal proliferative lesions of the breast. Intraductal proliferative lesions are a group of diverse proliferations that typically originate from the terminal duct-lobular unit and are confined to the mammary duct lobular system (Ellis et al., 2003). The three other categories besides DCIS include: a) usual ductal hyperplasia (UDH), which describes a benign ductal proliferative lesion typically characterised by secondary lumens, and streaming of the central cells, b) atypical ductal hyperplasia, which is described as a neoplastic intraductal lesion characterised by proliferation of evenly distributed monomorphic cells and c) flat epithelial atypia, a neoplastic intraductal alteration and characterized by replacement of the original epithelial cells by a single or several layers of mildly atypical cells (Ellis et al., 2003). Due to a lack of distinction in the literature between different intraductal proliferative lesion categories, focus shall be placed on DCIS.

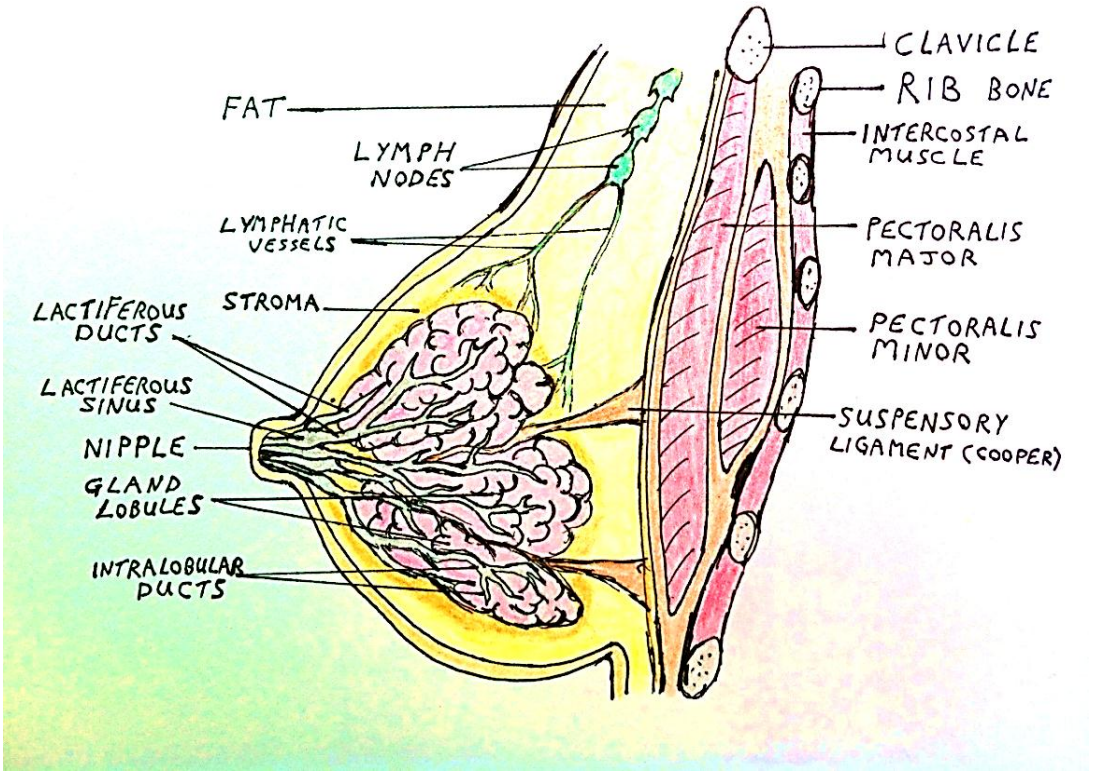


Figure 2.1 Anatomy of the female breast

DCIS includes a wide spectrum of diseases ranging from non-life threatening low-grade lesions to high-grade lesions that may harbour invasive breast cancer foci (Virnig et al., 2010). Histologically (investigation of the microscopic structure, composition and function of tissues and cells), it is characterized by a proliferation of malignant-appearing cells of the duct system and terminal lobular units of the breast (Leonard and Swain, 2004). DCIS varies in size and can be extensive, but has not spread outside the ductal basement membrane and thus, cannot have metastasised (Resetkova, 2012). It is classified according to its architectural pattern (solid, cribform, papillary and micropapillary), tumour grade (high, intermediate and low) and comedo (presence/absence of cells that appear cytologically malignant, with the presence of high-grade nuclei, pleomorphism and abundant central luminal necrosis) (Ellis et al., 2013; Vernig et al., 2010). DCIS accounts for around 20% of breast cancers detected by mammographic (x-ray of the breasts) screening (Virnig et al., 2010). In 2008, 2,500 cases of DCIS were

detected by screening in the UK (NHSBSP & ABS, 2010). DCIS is considered a precursor lesion to invasive breast cancer, with a relative risk (RR) of developing invasive breast cancer of 8.0 to 11.0 (Ellis et al., 2003). Post-DCIS diagnosis, the probability of a diagnosis of invasive breast cancer has been estimated at 5.3% within five years and 10.9% within 10 years (NBOCC, 2010).

The term LCIS was chosen to emphasis the morphological similarities between the cells of LCIS and invasive LCIS (Foote and Stewart, 1941). However, the term atypical lobular hyperplasia (ALH) is more appropriately used to describe morphologically similar but less well-developed lesions, and an all-encompassing term, lobular neoplasia (LN), is used to cover both ALH and LCIS (Haagensen et al., 1978). Morphologically LN is defined as a proliferation of generally small and often loosely cohesive cells originating in the terminal duct-lobular unit, with or without pagetoid (i.e. resembling Paget's disease, that is any deviation from or interruption of the normal structure or function of any body part, organ or system) involvement of terminal ducts (Tavassoli et al., 2003). The term ALH is used when there is an incomplete distension of the involved terminal duct-lobular units or when residual lumens are present, while LCIS is used to describe fully developed lesions (Lakhania et al., 2006). The true incidence of LN is difficult to establish because there are no specific clinical abnormalities, and in most cases it is undetectable by mammography. However, it has been estimated that its frequency ranges from less than 1% to 3.8% of all breast carcinomas (Tavassoli et al., 2003). LN has generally been considered a breast cancer risk indicator, conferring an increased rate of development of about 1–2% per year, a 10-year risk of 7-8%, with a lifetime risk (i.e. the risk of contracting breast cancer by the age of 85 years, estimated by cumulating all the annual risks over a woman's life span up to age 85) of 30–40% (Chuba et al., 2005; Bauer et al., 1994; Haagensen et al., 1978).

Women with LN range in age from 15 to over 90 years old, but most are premenopausal (Tavassoli et al., 2003).

When breast tumours infiltrate surrounding tissue they are defined as invasive (Pelengaris and Khan, 2009). Breast cancer results from a single transformed cell that proliferates at an unregulated rate and multiplies to form a growth of abnormal cells within the breast tissue. Within a normal human breast the lobules and ducts are lined with a double layer of epithelial cells, of which the inner layer of luminal cells and outer layer of basal cells are in direct contact with the basement membrane (an extracellular matrix lying between cells and underlying connective tissue). The transformation of different epithelial cells within the breast results in substantial heterogeneity in breast cancer subtypes (Holstege, 2010). Gene expression profiling, using techniques such as DNA microarrays and immunohistochemical markers, has classified invasive breast cancers into five distinct subtypes: 1) luminal A, which are oestrogen receptor (ER) positive and/or progesterone receptor (PR) positive, and human epidermal growth factor receptor 2 (HER2 or HER-2/*neu* or *erb*B2) negative; 2) luminal B, which are ER positive and/or PR positive, and HER2 positive; 3) HER2 overexpressing, which are ER negative, PR negative, and HER2 positive; 4) basal-like, which are ER negative, PR negative, HER2 negative, cytokeratin 5/6 positive and/or epidermal growth factor receptor (EGFR) positive; and finally 5) normal breast-like tumours, which have relatively high expression of gene expressions of adipose tissue and other non-epithelial cell types and relatively low expression of luminal cell types (Carey et al., 2006; Rakha et al., 2006; Sorlie et al., 2001; Perou et al., 2000). Luminal cancers are the most common invasive breast cancer, accounting for up to 70% of cases, HER2 and basal breast cancers account for approximately 15% of cases

each, while normal breast-like cancers may account for six to 10% of all breast cancers (Schnitt, 2010).

Breast cancer subtypes have different epidemiological risk factors and different natural histories, which in turn give rise to differences in clinical presentation, histology and responses to systemic and local therapies (Goldhirsch et al., 2011). However, at this time, the assessment of breast cancer subtype is not widely used. Instead the choice of therapy is based on patient's age, tumour size, histological grade, lymph node involvement, ER, PR and HER2 status (Shnitt, 2010). Better methods are therefore required in the future to aid the classification of these subtypes in order to help assess prognosis and determine the most appropriate treatment for patients on an individual basis.

2.1.2 Diagnosis and classification of breast cancer

Breast cancer may cause any of the following symptoms, a lump or thickening in or near the breast or in the underarm area, a change in the size or shape of the breast, a dimple or puckering in the skin of the breast, a nipple retraction, unusual discharge such as blood from the nipple, scaly, red or swollen skin on the breast, nipple or areola and dimples in the breast that look like the skin of an orange, called peau d'orange (Bevers et al., 2009). The majority of breast cancers are either detected by women themselves through self-examination, through clinical breast examinations or by mammography (Porth, 2011).

The diagnosis of breast cancer is based on clinical, radiological and pathological examinations. Clinical breast examinations involve bimanual palpation of the breasts and locoregional lymph nodes (NCI, 2013). If the clinician detects an abnormality the patient undergoes diagnostic imaging rather than screening.

Between 14% and 21% of breast cancers are detected by clinical breast examination (Jardines et al., 2013). Radiological examinations include bilateral mammography and ultrasound of the breast (and potentially the lymph nodes). Usually screening mammography can detect breast tumours two years before they are palpable (Banning, 2007), and represents a secondary prevention measure for the early recognition of breast cancer which is associated with improvements in outcomes (Porth, 2011). In the UK, women aged 50 to 70 years are automatically invited for mammographic screening every three years. Women over the age of 70 are still eligible for screening and by the end of 2012, all women in England aged 47 to 73 will be invited (Public Health England, 2013). Due to the diminished sensitivity of mammography when the breast tissue is dense, breast ultrasonography has been used as an adjunct to differentiate cystic from solid tissue in women with non-specific thickening (Jardines et al., 2013; Porth, 2011). In addition, magnetic resonance imaging (MRI) of the breast may be needed in cases involving diagnostic challenges arising, such as dense breast tissue especially in young women, familial breast cancer associated with breast cancer gene mutations, silicone gel implants, positive axillary lymph node status with primary tumor in the breast or where multiple tumor foci are suspected, in particular with lobular breast cancer (Sardanelli et al., 2010). Positron emission tomography (PET) and computer or digital mammography may also be useful diagnostic tools to supplement mammography with women with dense breasts or a strong family history of breast cancer and/or known breast cancer gene 1 (BRCA1) and breast cancer gene 2 (BRCA2) mutation carriers (Porth, 2011).

Pathological diagnosis involves fine needle aspiration, stereotactic (core) needle biopsy or incisional or excisional biopsy. Fine needle aspiration is a simple method, involving the aspirating of cells and attendant fluid with a small-bore

needle, used for obtaining material for cytologic (i.e. microscopic study of cells to determine their structure, and how they form and function) examination (ACS, 2013). It can identify the presence of malignant cells, but cannot differentiate between in situ and invasive cancer. In the past, in order to establish a histologic diagnosis of breast cancer either an excisional biopsy (removal of the whole tumour) or incisional biopsy (removal of a small part of a large tumour) was performed (ACS, 2013). Recently for diagnosis of a suspected malignancy, fine needle aspiration, incisional and excisional biopsies have been largely replaced as the preferred diagnostic tool by core biopsy. Core biopsy is performed using local anesthesia and guided by mammography. It involves the removal of a small cylinder of tissue (about 0.16 to 1.27 cm), and cells are available for histological evaluation with 96% accuracy in detecting cancer (ACS, 2013). Biopsy specimens are then used to grade and stage breast cancers to determine the likely rate of tumour growth and spread, estimate prognosis and determine the most effective treatment regimen. In addition to grading and staging of breast cancer, ER, PR and HER2 receptors analysis is carried out on surgical specimens. The presence or absence of ER, PR and HER2 receptors can be used in predicting the responsiveness of tumours to hormonal manipulation (Porth, 2011). High levels of ER and PR improve the prognosis and increase the likelihood of remission (i.e. a decrease in or disappearance of signs and symptoms of cancer), while HER2 receptor overexpression is associated with a worse prognosis.

The grading of a breast tumour based on its histological and cytological characteristics and staging according to the clinical spread of the disease are the basic methods of classifying breast cancer. Tumour grade is determined based on how abnormal the tumour tissue and cells look under a microscope, and is used as a prognostic factor because it provides an indication of how quickly a tumour

might grow and spread (NCI, 2013). Breast cancer has its own grading systems, and the most commonly used system is the Nottingham grading system (Elston and Ellis, 1991). This system grades breast tumours based on tubule formation (or gland or acinus formation), which determines how much of the tumour tissue has normal breast duct structures, nuclear grade (or nuclear atypia or pleomorphism), which evaluates the size and shape of the nucleus in the tumour cells and mitotic (i.e. division of somatic cells) rate, which describes how many dividing cells are present (which is a measure of how fast the tumor cells are growing and dividing) (AJCC, 2010). Each category is scored between one and three, where a score of one represents that cells and tumour tissue that are “well-differentiated”, or the cells of the tumour and the organization of the tumour’s tissue are most similar to normal cells and tissue, and a score of three means the cells and tumour tissue are “poorly differentiated”, or they look the most different from normal cells and tissue and grow and spread at a faster rate than well-differentiated tumours (NCI, 2013). The three values from the categories are then added together to produce scores of three to nine. Based on these scores three grades are possible; G1 or low grade (i.e. well differentiated) from a total score of 3–5; G2 or intermediate grade (i.e. moderately differentiated) from a total score of 6–7; and G3 or high grade (i.e. poorly differentiated) from a total score of 8–9 (Ollis et al., 2003).

The staging of cancer is important in order to determine the prognosis of patients and deciding upon the most appropriate treatment and comparing different treatment regimens (Porth, 2011). Most staging systems are based on identifying the tissue of origin regardless of organ location, and focus on the similarities in cellular structure and function among tumours. The majority of adults with solid tumours are staged using the internationally recognised Tumour, Node, Metastasis (TNM) classification system (UICC, 2010) (see appendix A). The TNM

classification system is a measure of the extent of disease, and is used to guide management and determine prognosis (AJCC, 2010). In addition to assessing the extent of the primary tumour, the TNM classification assesses the involvement of lymph glands and the presence of metastases. The system is a “bin model”, in which patients are partitioned using TNM prognostic factors, so that each patient is placed in only one bin, and these bins are grouped together into larger bins called stages (Burke, 2004). It is based upon retrospective analyses of survival in diverse samples of patients representing all stages of disease. For example, if a new patient is placed in the T1, N1, M0 bin, then that patient’s 5-year disease specific survival is predicted to be the same as the mean survival of patients placed in that group years earlier (UICC, 2010; Burke, 2004). The prognostic value of the TNM system was revaluated for its latest 7th edition based on 211,645 breast cancer cases diagnosed between 2001 and 2002 and entered into the National Cancer Data Base (UICC, 2010).

The TNM staging system has been useful for assessing prognosis and risk in groups of breast cancer patients, but has had limited success in determining prognosis and risk in individual patients (Schnitt, 2010). This system assumes the contiguous spread of disease over time (temporal determinism) (Burke, 2004). However, ordering does not take into account which patients received adjuvant therapy, for example, staged IIB patients who do not undergo adjuvant therapy may have a worse prognosis than stage IIA who have received adjuvant therapy. If a bin with a better prognosis is placed below a bin with a worse prognosis the validity of the system would be questioned. Furthermore, the early detection of disease due to improved screening has resulted in an increase in the number of patients in the early stages and a reduction in the number of patients in the later stages, and changes to surgery and neoadjuvant therapy has further reduced the

size of tumours, detection of nodal metastases and the accurate grading of tumours (Burke, 2004). The above factors lead to a reduction in the predictive ability of the staging system. In addition to these issues, the TNM system does not accommodate continuous biomarkers or the addition of new biomarkers, which can improve the accuracy of prognosis predictions (Burke, 2004). The problems presented above have led some researchers to call for a move away from temporal determinism to one of biological determinism (Burke, 2004). This approach accepts that carcinogenesis is defined by the characteristics of the tumour and the host, and that treatment should be driven by the molecular biology of the tumour or the host and not the tumours location at detection. The finding that invasive breast cancer is not a single disease but a group of several tumour subtypes has been crucial in developing an understanding of differing breast cancer prognosis and responses to treatment in individuals within each staging category.

Table 2.1 Surrogate definitions of intrinsic subtypes of breast cancer (adapted from Goldhirsch et al., 2011)

Intrinsic Subtype	Clinico-pathologic definition
Luminal A	**Luminal A** • ER and/or PR positive • HER2 negative • Ki-67 low (< 14%)
Luminal B	**Luminal B (HER2 negative)** • ER and/or PR positive • HER2 negative • Ki-67 high
	Luminal B (HER2 positive) • ER and/or PR positive, • any Ki-67 • HER2 over-expressed or amplified
HER2 (Erb-B2) overexpression	**HER2 positive, non-luminal** • HER2 over-expressed or amplified • ER and PR negative
'Basal-like'	**Triple negative (ductal)** • ER and PR negative • HER2 negative

The 12th St Gallen International Breast Cancer Conference Expert Panel adopted a new approach to breast cancer subtype classification based largely on the subtypes classification outlined earlier in this section. However, for practical purposes the panel (Goldhirsch et al., 2011) proposed that subtypes may be approximated using clinicopathological rather than gene expression criteria. This new classification is based on expression of ER, PR, HER2 and Ki-67 (a monoclonal antibody used to assess uncontrollable cell proliferation). The panel reached the following consensus on breast cancer subtypes, 1) luminal A; 2) luminal B (HER2 negative); 3) luminal B (HER2 positive); 4) HER2 overexpression (HER2 positive, non-luminal); and finally, 5) Basal-like (triple negative, ductal) (Goldhirsch et al., 2011). The full subtype classification is provided in table 2.1. The differences between each of these subtypes imply that clinician's should consider breast cancer cases within the various distinct subtypes in order to properly assess the relevant evidence and arrive at appropriate therapeutic advice. The use of breast cancer subtypes to guide treatment decision may offer an advantage over the classification systems such as the TNM system, as it allows treatment to be driven by the molecular biology of the tumour or the host rather than the tumours location at detection.

2.2 Epidemiology of Breast Cancer

Cancer is a major health issue of our day (Pelengaris and Khan, 2013). Of the estimated 57 million global deaths in 2008, non-communicable diseases, including cardiovascular diseases (CVD) and certain cancers, were responsible for an estimated 36 million deaths worldwide, with 17 (~30% of all deaths) and 7.6 (~13% of all deaths) million deaths attributable to CVD and cancer, respectively (Jemal et al., 2011). The number of global cancer deaths is projected to almost double to 13 million by 2030. Breast cancer is the most frequently diagnosed cancer and a

leading cause of cancer death among females, accounting for 23% (1.38 million) of total cancer cases and 14% (458,400) of cancer deaths in 2008 (Jemal et al., 2011). Thus, cancer is a major and increasing disease burden worldwide and breast cancer represents the largest cancer burden for women.

2.2.1 Breast cancer prevalence

Cancer prevalence is expressed as the number of people or the proportion of the population who are alive on a specified index date and have previously been diagnosed with cancer (i.e. cancer survivors) (Maddams et al., 2009). Prevalence is used as an indicator of the burden of cancer and can help to inform health care service planning. Prevalence figures are presented as simple counts of patients as well as crude and age-standardised proportions (ASP). Crude proportions are calculated by dividing the number of patients who live in a given area by the population of that area. The ASP calculation takes into account the age composition and size of a population to allow comparisons between different areas to be made (Parkin, 2006). Because cancer is much more common in the elderly, a more elderly population will in general have a higher crude proportion. Therefore, ASPs should be used to account for differences in the age distribution. ASPs are most commonly standardised using the European Standard Population or World Standard Population statistics.

The number of persons diagnosed and living with cancer within a five-year period (i.e. five-year prevalence) has increased from 22.4 million in 2000 to 28 million in 2008 (Ferlay et al., 2000; Ferlay et al., 2010). Worldwide, female only breast cancer has the highest five-year prevalence of all cancers, with nearly 5.2 million women (World ASP=210.7 per 100,000) diagnosed and still living between 2003 and the end of 2008 (Ferlay et al., 2010).

Cancer prevalence is influenced by both the number of new cases each year and survival. One-year prevalence is strongly associated with incidence, whereas five-year and ten-year prevalence is associated with both incidence and survival. The most recent UK cancer prevalence data comes from the National Cancer Intelligence Network (NCIN, 2011). The NCIN (2011) presented one-year, five-year and ten-year prevalence of cancer in the UK for the end of 2006. There were over 200,000 prevalent cancer patients who were less than a year post-diagnosis, at the end of 2006, representing a 5% increase in prevalence compared to the NCIN's previous report (2006). Overall, there were 1.13 million cancer survivors (European ASP=1,501 per 100,000 population) in the UK who had been diagnosed with cancer in the ten years before the end of 2006. In the UK, breast cancer was the most prevalent female cancer. At the end of 2006, the number of women that were within one year of breast cancer diagnosis was 40,137 (108.8 per 100,000), while the five-year prevalence was 175,974 women (475.6 per 100,000) and the ten-year prevalence was 296,037 women (790.8 per 100,000).

2.2.2 Breast cancer incidence

Cancer incidence is expressed as the number of new cases of cancer diagnosed for a given period, usually a year (Stewart and Kleihues, 2003). The statistics are generally provided as the total number of cases or similar to prevalence proportions, incidence rates can be crude or age-standardised (AS) using the European Standard Population or World Standard Population statistics. The global number of new cases of cancer is increasing. In 2000, there was an estimated 10.1 million new cases of cancer, while in 2008 new cancer cases increased to 12.4 million, and this is projected to rise to 21.4 million in 2030 (Ferlay et al., 2000; Ferlay et al., 2010). There were almost 1.4 million new cases of female breast cancer worldwide in 2008, with a world AS incidence rate was 66.4 per 100,000

population in developed countries and 27.3 per 100,000 population in less developed areas (Jemal et al., 2011).

In 2008, the UK had the 22nd highest cancer incidence in the world (World AS rate=266.9 per 100,000) (Ferlay et al., 2010). According to the latest data from the Office of National Statistics (ONS, 2012), there were on average 315,100 (158,900 males and 156,300 females) cases of newly diagnosed cancer each year in the UK during the period 2007 to 2009 (see figure 2.2). These data represented an increase in the average number of newly diagnosed cases of cancer (147,000 males and 146,000 females) when compared to the period of 2004 to 2006 (ONS, 2012; ONS, 2009). Furthermore, the yearly incidence of cancer in England is predicted to increase by 33%, from 224,000 cases in 2001 to 299,000 in 2020 (Moller et al., 2007).

On average there were 47,809 new incidences of breast cancer each year in the period of 2007 to 2009 (ONS, 2012). UK women had the 9th highest breast cancer incidence rate (world AS=81.9 per 100,000 population) in the world in 2008 (Ferlay et al., 2010). In the UK, breast cancer had the highest incidence rate of all cancers, with an average European AS rate of 124.2 cases per 100,000 population each year between 2007 and 2009 (ONS, 2012). This represented a slight increase in incidence compared to 2004 to 2006 figures (122 per 100,000) (ONS, 2009). Recent projections have estimated that new cases of breast cancer in England will rise to 49,743 cases in 2020, representing a 44% increase from 2001 figures (Moller et al., 2007).

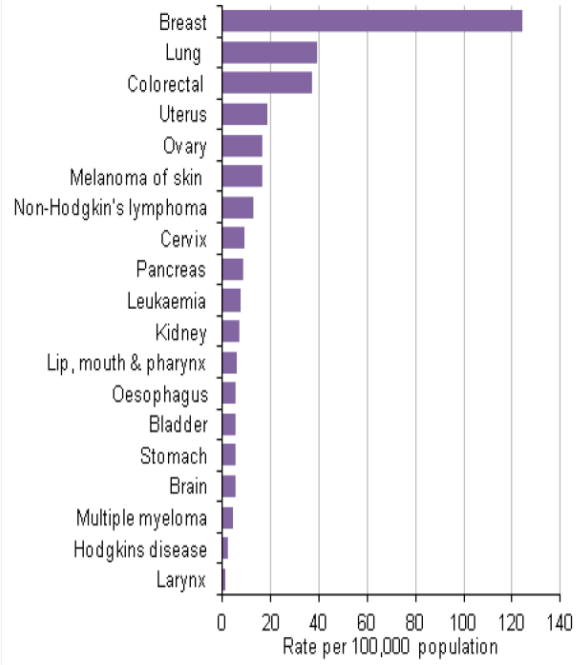


Figure 2.2 UK age-standardised incidence for the major cancers in females, 2007-2009 (ONS, 2012)

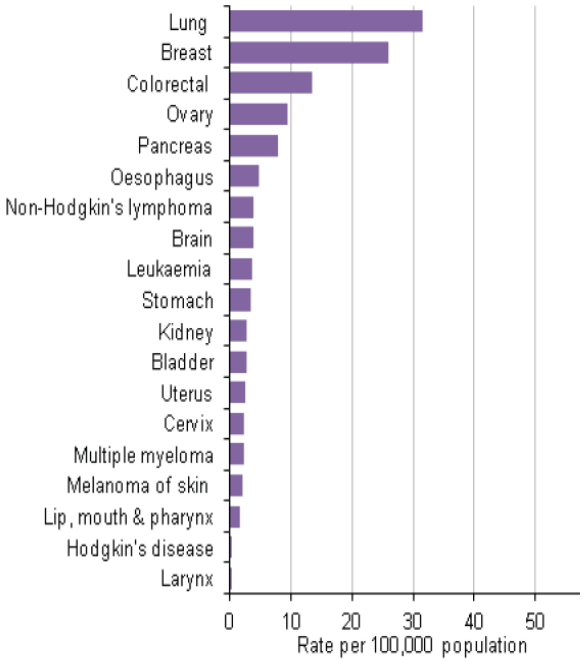


Figure 2.3 UK age-standardised mortality for the major cancers in females, 2007-2009 (ONS, 2012)

2.2.3 Breast cancer mortality

Mortality is the number of deaths which have occurred, and the mortality rate is the number of deaths per 100,000 persons per year (Stewart and Kleihues, 2003). Global cancer mortality rates have increased from 6.2 million deaths in 2000 to 7.6 million deaths in 2008 (Ferlay et al., 2000; Ferlay et al., 2010). Deaths from cancer worldwide are projected to continue rising, with an estimated 13.1 million deaths in 2030 (Ferlay et al., 2010). There was an estimated 458,400 deaths worldwide attributed to breast cancer, and world AS mortality rates for breast cancer was higher in more developed countries compared to less developed countries (15.3 and 10.8 per 100,000 population, respectively) (Jemal et al., 2011).

Between the years of 2007 and 2009, there were on average 156,200 deaths (81,600 male and 74,600 female deaths, respectively) from cancer each year in the UK (see figure 2.3; ONS, 2012). The equivalent European AS mortality rates

were 209 per 100,000 deaths for males and 151 per 100,000 deaths for females (ONS, 2012). These mortality rates were higher than those in the period of 2004 to 2006, on average 154,000 (80,000 males and 74,000 females) died from cancer in each of these years in the UK, corresponding to an AS mortality rate of 218 and 155 per 100,000, respectively. Breast cancer was second only to lung cancer as the cause of deaths from cancer in UK females (European AS mortality rate of 26.1 and 31.5 per 100,000, respectively). In the UK in 2008, 12,122 women died of breast cancer. The average mortality rate for breast cancer in 2007-09 was slightly lower than that of 2004 to 2006 (European AS mortality rate of 26.1 and 28.3 per 100,000, respectively) (ONS, 2012; ONS, 2009).

2.3.4 Breast cancer survival

Cancer survival rates in a population are affected by a number of factors, most importantly, the types of cancer that occur, the stages at which cancers are diagnosed and whether treatment is available (ACS, 2011). Survival rates can be expressed in relative or net terms. Relative survival is the ratio of the observed survival and the survival that would have been expected if cancer patients had only experienced the background mortality (defined by general population life tables) experienced by the general population. It can be interpreted as the survival of cancer patients after other causes of death are taken into account (Walters et al., 2009). Net survival on the other hand, is estimated with an excess hazard model, in which the all-cause mortality is modelled as the sum of the cancer-related (excess) mortality hazard and the background (expected) mortality (Nur et al., 2011). Similar to relative survival, the net survival in a population of cancer patients is their survival from the cancer of interest in the absence of other causes of death (Nur et al., 2011).

Table 2.2 Five-year Relative Survival Rates (%) for Breast Cancer among Individuals† aged 15 and older in select countries

	England (1995-1999)	**United States (1999-2006)**	**Austria (1995-1999)**	**Poland (1995-1999)**	**China (1990-2001)**	**India (1990-2001)**	**Uganda (1990-2001)**
Relative survival rates* (%)	77.3	89.0	80.0	73.7	82.0	52.0	46.0

* Survival rates are age standardised. Variations in survival rates across countries may reflect differences in detection practice, availability of treatment and data quality.
† Survival rates for Asia and Africa are for person's aged 0-74.

In England, the AS relative survival rate for all cancer site for this period (1995-99) was 46.2%. For breast cancer, the five-year (1995-99) AS relative survival rate in England was 77.3%. AS relative survival rates in England have improved substantially since then, the AS five-year relative survival for women (15-99 y) diagnosed with breast cancer during 2001-06 and followed up in 2007 was 81.1%, and rose to 82% during the period of 2000 to 2004 and followed up in 2005 (Walters et al., 2009). Net breast cancer survival rates in England have also improved, increasing from 90.8% in 1996 to 95.7% in 2009 (Nur et al., 2011).

The statistics presented in this section highlight the major and growing burden of cancer across the world. Both in the UK and worldwide the prevalence and incidence of cancer, and particularly relevant to this thesis, breast cancer, is growing ever larger. In the UK there are now more women being diagnosed with breast cancer each year, and positively, with decreasing mortality rates there more women living with breast cancer within five years of diagnosis than there has ever been since records began. Incidence and survival rates are projected to rise even further in the future. Therefore, there are more women who require diagnostic,

therapeutic, supportive or palliative services than ever before. This poses a major threat to already stretched healthcare services. The Department of Health (2010) has recognised this and has emphasised in their “Cancer Reform Strategy” that identifying and addressing the requirements of cancer survivors in UK is a high priority.

2.3 The aetiology and pathogenesis of breast cancer

The aetiology (i.e. causes) of breast cancer can be viewed from two perspectives. The first perspective entails an investigation of genetic and molecular mechanisms that characterise the transformation of a normal cell into a cancerous cell, while the second involves an examination of external factors such as age, heredity and environmental factors that contribute to its pathogenesis (development) and progression. The first part of this section therefore, includes an exploration of the genetic and molecular mechanisms that might explain the origins of cancer cells and a description of the development and progression of breast cancer. The second part includes a comprehensive review of the literature pertaining to the factors associated with the risk of developing familial and sporadic breast cancer and a quantification of the level of risk presented by these factors.

2.3.1 Genetic and molecular aetiology of breast cancer

All cancers are genetic diseases of somatic cells (Knudson, 2001). They begin with a mutational event, or in other words a permanent change in the DNA sequence of a gene in a single cell. This alteration in the DNA coding allows the cell to overcome the intrinsic and extrinsic restraints imposed on cells within the adult organism, and in the case of cancerous cells allows the cell to multiply uncontrollably and do so in places where it should not (Khan and Pelengaris, 2013). Along with the original mutation, subsequent generations acquire further

mutations when they divide, and almost universally lose normal DNA repair processes, which helps explain why tumours develop from benign growths to malignancy (Kinzler and Vogelstein, 1996).

The transformation of a normal cell into a cancerous one has been described in three main stages, namely, initiation, promotion and progression (Porth, 2011). Initiation describes the irreversible stage in which the cell is altered through exposure to appropriate doses of a carcinogenic agent, in such a way that it has a neoplastic potential. The promotion stage describes the potentially reversible process where potentially malignant cells, which have already undergone initiation, go into a phase of excessive growth mediated by various chemical and growth factors. The progression stage involves the process by which tumour cells acquire invasiveness, metastatic competence, autonomous growth and increased genetic instability. This classification does not exclude the possibility that each of the stages, in the natural state, may depend on one or several changes in the genetic make-up (genotype) of the cells.

As normal cells evolve progressively towards a neoplastic state, they acquire a number of capabilities driven by the need of cancer cells to acquire traits that enable them to become tumorigenic and ultimately malignant (Hanahan and Weinberg, 2011). Hanahan and Weinberg (2000) proposed six hallmarks of cancer that comprised of six biological capabilities acquired during the development of human cancer. These include sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis and activating invasion and metastasis. The acquisition of these hallmarks is expedited by increasing genome instability. In an update, Hanahan and Weinberg (2011) added two emerging hallmarks to this list, namely,

reprogramming of energy metabolism and evading immune destruction. Adding a further dimension of complexity, tumours contain both cancer cells and a collection of recruited, normal cells that contribute to the acquisition of hallmark traits by creating the “tumour microenvironment” (Hanahan and Weinberg, 2011). These acquired hallmark traits of tumours allow single somatic cell mutations to develop into malignant cancer tumours by increasing proliferation, resisting death, by providing an environment in which cells can replicate uncontrollably and ultimately activating invasion of surrounding tissues and metastasis from its site of origin to other locations within the organism. The mechanisms for the development of these hallmarks in breast cancer will be discussed below.

The transformation of a normal breast cell into a cancerous cell is thought to be a result of changes in cell physiology originating from genetic damage or mutations. The genes associated with cancers are classified into two broad categories. The first category includes “proto-oncogenes”, which are normal genes that become cancer-causing “oncogenes” if mutated and as a result become overactive. The second category comprises of “tumour-suppressor genes”, which by being less active can create an environment in which cancer is promoted (ACS, 2011).

Proto-oncogenes encode for normal cell proteins such as growth factors (responsible for regulating the division and proliferation of cells), growth factor receptors, growth factor signalling molecules (responsible for transmitting information between cells) and transcriptional factors (responsible for turning particular gene expressions “on”) that promote cell growth and increase growth factor-dependent signalling (Lodish et al., 2000). There are a number of genetic events that can cause a mutation which can transform a proto-oncogene into an oncogene. Gene amplification is a common event in breast cancer, and involves

the multiple copying of certain genes which may cause overexpression with higher than normal levels of proteins that promote cell proliferation. In breast cancer, genomic amplification of the HER2 proto-oncogene results in elevated levels of HER2, and is seen in about 20% of primary invasive breast cancer cases (Wolff et al., 2007). Overexpression of HER2 is associated with an aggressive tumour type and a negative clinical prognosis in both lymph-node positive (Ravdin and Chamness, 1995; Antoniotti et al., 1994; Mansour et al., 1994) and node-negative breast cancer patients (Andrulis et al., 1998).

Another genetic event that can cause or activate oncogenes is point mutation, which is when a single nucleotide base of DNA changes due to an insertion, deletion or substitution. An example of this type of mutation is seen in the RAS oncogene, which is common in lung, colorectal and pancreatic cancer but relatively rare in breast cancer (Fernández-Medarde and Santos, 2011). Other mechanisms of oncogene activation include chromosomal translocation, which involves the translocation (swapping) of chromosomal arms between heterologous chromosomes (i.e. chromosomes which differ in type, function or size) which results in abnormal expression of the translocated genes, the formation of a unique fusion gene or the inactivation of tumour suppressor genes (Nambiar and Raghavan, 2011). All of these outcomes could promote uncontrolled cell proliferation or influence apoptosis. Chromosomal translocation may contribute to the mutational burden of many breast cancers, but further research is needed to elucidate the contribution of this type of mutation in breast cancer development (Stephens et al., 2009).

Tumour suppressor genes are genes that normally help prevent unrestrained cellular growth and promote DNA repair and cell cycle checkpoint activation, which

slows or arrests cell-cycle progression, thereby allowing time for appropriate repair mechanisms to correct genetic lesions before they are passed on to the next cellular generation (Lee and Muller, 2010; Abraham, 2001). Therefore, loss of function mutations in these genes prevents normal DNA repair and promotes unregulated cell proliferation. Mutations of tumour protein 53 (p53), perhaps the most studied tumour suppressor gene are estimated to occur in up to half of all human cancers and in 20 to 30% of breast cancers (Hollstein et al., 1991). The p53 gene normally acts to prevent the propagation of genetically damaged cells by detecting DNA damage and assisting the repair process by arresting the cell cycle in G1 (phase of cell growth) and inducing DNA repair or apoptosis if repair is not possible. The loss of p53 prevents the repair of DNA, leading to the acquisition of mutations during cell division and ultimately to malignant transformation (Porth, 2011). Other tumour suppressor gene mutations which have a major role in breast cancer development include mutations in the BRCA1 and BRCA2 genes, which are normally involved in DNA repair. These two genes will be discussed in more detail in the discussion of familial breast cancer (section 2.4).

In addition to oncogenes and tumour suppressor gene mutations, micro ribonucleic acid (miRNA) genes can promote the transformation from normal cell function to malignancy. Instead of encoding proteins, these genes produce a single strand of RNA, known as miRNA, which serves to regulate gene expression (Porth, 2011). Many miRNA can be found in chromosomal regions that undergo rearrangement, deletions and amplifications (Zhang et al., 2013). MiRNA can either block protein translation or prevent degradation of messenger RNA (mRNA), which carries codes from the DNA to the protein synthesising ribosomes in the cytoplasm of cells, by pairing with an mRNA that complements the sequence of

mRNA (Dvinge et al., 2013). Furthermore, miRNAs can upregulate (i.e. increase activity) or downregulate (i.e. decrease activity) cancer cells (Zhang et al., 2013).

There is considerable evidence indicating that miRNAs play important roles in cell proliferation, apoptosis and differentiation (Zhang et al., 2013; Casalini and Iorio, 2009; Brennecke et al., 2003). Depending on the context, they may function as either tumour suppressors or oncogenes (Esquela-Kerscher et al., 2006). Overexpression of oncogenic miRNAs by amplification may deregulate (i.e. loss of regulation) the target tumour suppressor gene, whereas underexpression of tumour suppressor miRNAs by deletion of the miRNA locus can result in the upregulation of a target oncogene (Caldas and Brenton, 2005). A number of miRNAs are deregulated in breast cancer. For example, deregulation of the miRNA, miR-125b, has been observed in invasive breast cancer (Scott et al., 2007). Scott and colleagues (2007) reported that miR-125b suppressed cell proliferation by downregulation of HER2 and HER3 in breast cancer. Breast cancer subtypes have deranged miRNA expression signatures, which means miRNAs could potentially be used to devise novel molecular classifications of breast cancer and ultimately could facilitate the development of more individualised treatment strategies for breast cancer patients (Khoshnaw et al., 2009).

As well as mechanisms involving DNA and changes to chromosomal structure, carcinogenic changes can be induced through epigenetic mechanisms, which involve changes in patterns of gene expression without any alterations in the DNA sequence (Esteller, 2008). Epigenetic mechanisms may “silence” genes (i.e. interrupt/suppress the expression of a gene at transcriptional and translation levels), such as tumour suppressor genes so that the gene although still present is

not expressed and a cancer-suppressing protein is not synthesised (Porth, 2011). Epigenetic mechanisms that lead to gene silencing include DNA methylation, histone modification, miRNA expression and higher order chromatin structure. Methylation, which involves the addition of a methyl group to a cytosine nucleotide in DNA, of the promoter region of the DNA (region which the transcription of a gene is initiated) prevents transcription and causes gene inactivity (Esteller, 2008). Abnormal patterns of methylation have been found in several types of breast cancer (Vo and Mills, 2012). In sporadic (non-familial) breast cancers mutations in oncogenes are rare, however, epigenetic gene silencing by DNA hypermethylation of BRCA1, which prevents BRCA1's role in DNA repair, is observed frequently (Heyn et al., 2013). Furthermore, there is a suggestion that DNA hypermethylation resulting from high alcohol consumption and low folate intake has been indicated in the development of breast cancer (Christensen et al., 2010). Genes silenced by hypermethylation can be inherited, and epigenetic silencing can be considered a "first hit" in non-familial breast cancer or as a "second hit" when DNA hypermethylation occurs in individuals with inherited cancer (Esteller et al., 2001; Grady et al., 2000).

2.3.2 Pathogenesis of breast cancer

Recent advances in genetic, transcriptomic and epigenetic technologies combined with advanced microdissection and ex vivo isolation techniques have provided a more detailed understanding of the pathological progression of breast cancer subtypes. Observations from epidemiological and morphological studies led to the formulation of the classic model of breast cancer initiation, transformation and progression. For the ductal subtype, a normal epithelial cell was traditionally thought to progress to flat epithelial atypia, atypical ductal hyperplasia and DCIS, before evolving into invasive ductal carcinoma and potentially metastatic cancer

(Bombonati and Sgroi, 2011). While for the lobular subtype, the traditional model involves the progression from normal epithelium to the development of atypical lobular hyperplasia, LCIS, invasive lobular carcinoma and to potential metastases (Bombonati and Sgroi, 2011).

It now appears that human breast cancers progress along two distinct molecular genetic pathways that strongly associate with a low or high tumor grade (Bombonati and Sgroi, 2011). The low-grade pathway is characterized by recurrent chromosomal loss of 16q, gains of chromosome 1q, a low-grade-like gene expression signature and the expression of ER and PR. The progression along these pathways culminates with the formation of low and intermediate grade invasive ductal and invasive lobular carcinomas (see figure 2.4). Tumours resulting from the low-grade pathway consist of either luminal A (HER2 absent) or luminal B (HER2 present). The high-grade pathway is characterized by recurrent chromosomal gain of 11q13 and loss of 13q, a high-grade-like gene expression signature, amplification of 17q12 and a lack of ER and PR expression. Progression along the pathway includes intermediate- and high-grade ductal carcinomas that are stratified as HER2 or basal-like dependent on the expression/amplification of HER2.

The mechanisms underlying the pathogenesis of breast cancer are complex and vary among individual tumours (Gasparini et al., 2005). Mechanisms include defects in DNA repair mechanisms, disorders in growth factor signalling pathways, evasion of apoptosis, development of angiogenesis and the initiation of metastasis.

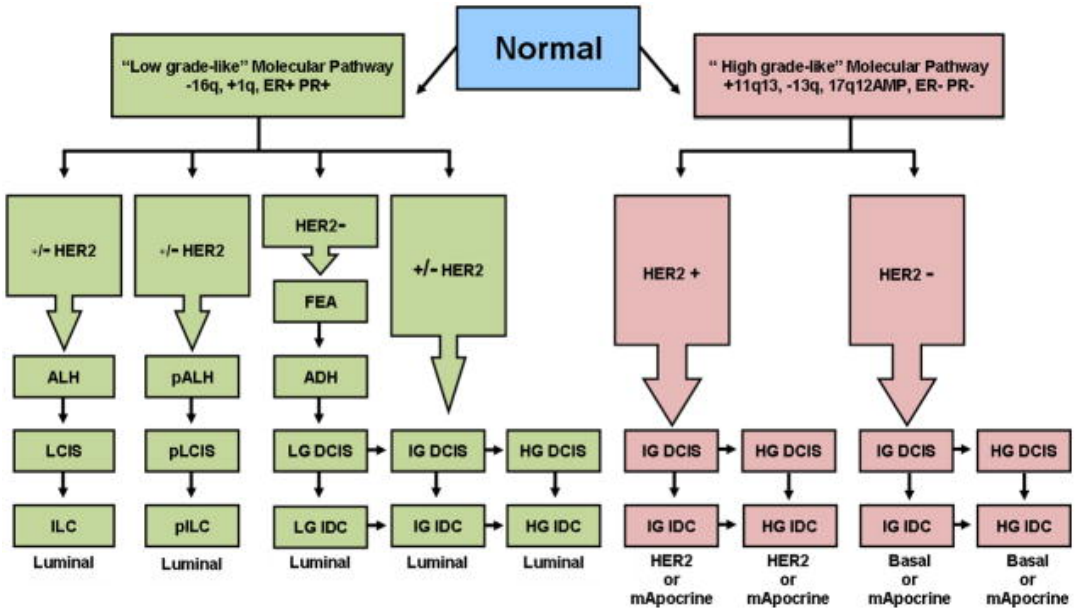


Figure 2.4 Divergent evolutionary pathways of breast cancer progression (Bombonati and Sgroi, 2011)

DNA repair genes influence cell proliferation and survival indirectly through their ability to repair non-fatal damage in other genes including proto-oncogenes, tumour suppressing genes and gene that control apoptosis (Porth, 2011). Exposure of cells to physical and chemical agents results in DNA damage, which can potentially cause a loss of genetic stability and elevated cancer risk. The action of particular DNA repair enzymes, encoded by genes involved in DNA repair, restore the Integrity of the damaged DNA (Vettriselvi et al., 2007; Charames and Bapat, 2003). Lower DNA repair capacity has been associated with a higher cancer risk (Matta et al., 2013). Mutations in genes involved in DNA repair can speed up the accumulation of mutations in these critical other genes. Genes implicated in breast cancer oncogenesis involved in DNA repair include p53, BRCA1, BRCA2 and ataxia-telangiectasia mutated (ATM) (Venkitaraman, 2001). In particular deficiencies in the type of DNA repair known as Nucleotide Excision Repair (NER) have been associated with breast cancer incidence, suggesting that

NER deficiency may contribute to the aetiology and development of sporadic and familial breast cancers (Latimer et al., 2010).

Mutations in genes that control signalling pathways are another relatively common pathway by which cancerous cells gain autonomous growth (Porth, 2011). These signalling pathways allow communication between growth factor receptors and their targets in the cell nucleus. In normal conditions, cell proliferation results from the binding of a growth factor to its receptor located on the cell plasma membrane, which activates the growth factor receptor resulting in the transfer of a signal across the cytoplasm to the nucleus via signal-transducing proteins that function as second messengers (Striker and Kumanr, 2011). The transfer of the signal to the nucleus triggers the induction and activation of regulatory factors that initiate DNA transcription and entry into the cell cycle. Many of the proteins involved in signalling pathways exert their influence through enzymes known as kinases, which add phosphates to proteins.

Altered patterns of gene expression can influence the activity of specific growth factor signalling pathways, and aberrant signalling is a key characteristic of cancerous cells that can lead to continuous proliferation and suppressed apoptosis (Lo and Hung, 2006). Pathways that have been identified as having aberrant signalling networks critical to the development and progression of breast carcinomas include HER family of receptor tyrosine kinases (including epidermal growth factor receptor, or EGFR/HER1, HER2, HER3 and HER4), ERs, BRCA 1/2, c-myc, transforming growth factor (TGF)-α and Wnt (Rosen et al., 2010; Lo and Hung, 2006). For example, the EGFR signalling pathway regulates growth, survival, proliferation, and differentiation in breast epithelial cells (Oda et al., 2005). EGFR is known to transmit extra-cellular mitogenic signals, such as EGF

and TGF-α, through activating a number of downstream signalling cascades, which results in altered gene activities, leading to uncontrolled tumour proliferation and avoidance of apoptosis (Lo et al., 2006). EGFR is highly expressed particularly in triple negative breast cancers (Eccles, 2011).

The proliferation of cancer cells occurs as a result of mutations in genes that regulate cell apoptosis. Under normal conditions, breast development is controlled by a balance between cell proliferation and apoptosis (Parton et al., 2001). Apoptosis is activated by specific enzymes known as caspases, which are also involved in the execution of the cell (Wong, 2011). Three pathways are known to activate caspases. The intrinsic (or mitochondrial) and extrinsic (or death receptor) pathways of apoptosis lead to a common pathway (the execution phase) of apoptosis, while a third less well-known initiation pathway is the intrinsic endoplasmic reticulum pathway (Wong, 2011). The failure of cancer cells to undergo apoptosis is thought to occur due to a disrupted balance of pro-apoptotic and anti-apoptotic proteins due to an over- or under-expression of certain genes, reduced caspase function and impaired death receptor signalling.

The p53 is a tumour suppressor gene that plays a key player in cell cycle regulation, development, differentiation, gene amplification and also the induction of cell apoptosis. In breast cancer, ER suppresses several p53 target genes implicated in the p53-mediated cell death response including activating transcription factor (ATF3), B-cell translocation gene (BTG2) and tumour necrosis factor receptor (TNFR) associated factor 4 (TRAF4) (Bailey et al., 2012). ATF3 negatively regulates cell-cycle progression and augments the transcription of p53 target genes, thus, its repression by ER would contribute to further inhibition of the p53 responses (Karmakar et al., 2009). BTG2 is regulated in response to DNA

damage in a p53-dependent manner, and has been found to inhibit breast cancer cell growth and to be downregulated by ER. Loss of BTG2 gene expression is associated with a poor prognosis in breast cancer patients and is a strong predictor of tumour grade and size, invasion, recurrence and overall survival (Möllerström et al., 2010). TRAF4 is a target gene of p53 which has been indicated in the p53-mediated cell death response, is known to be suppressed by ER (Bailey et al., 2012). There are numerous possible ways by which breast tumours lose normal apoptotic pathways, but all contribute to tumour development and progression by allowing DNA-damaged cells to survive and pass on their mutations to subsequent generations of daughter cells.

Even with genetic abnormalities described above, tumour growth would not be possible without angiogenesis to supply them with blood vessels. Angiogenesis allows a tumour to exceed a volume of 1-2 mm^2, and also provides a route for cancer cells to spread to distant organs (Langley and Fidler, 2007). Thus, angiogenesis is a prerequisite to both tumour growth and metastasis (Folkman, 1971). The exact molecular basis for the angiogenesis switch is unknown but appears to involve an increased production of angiogenic factors or loss of angiogenic inhibitors (Porth, 2011). For example, hypoxia is a key signal for the introduction of angiogenesis, and hypoxia-inducible factors (HIF) are angiogenic factors which are expressed increasingly from the progression of normal breast tissue to invasive carcinoma (Schneider and Miller, 2005). HIF expression is greater in higher grade tumours (i.e. poorly differentiated tumours) and is associated with increased cell proliferation and expression of ER and vascular endothelial growth factor (VEGF) (Bos et al., 2001). VEGF, a potent angiogenic cytokine, stimulates breast endothelial cell proliferation and induces angiogenesis, and is associated with reduced disease-free and overall survival (Byrne et al.,

2007; Gasparini et al., 1997; Obermair et al., 1997). The tumour suppressor gene, p53, under normal conditions represses the expression of pro-angiogenic factors, such as VEGF. However, when p53 activity is lost as is the case in some breast tumours, pro-angiogenic switches are overexpressed (Iovino et al., 2008).

Metastasis is the final stage of multi-step tumour progression, and describes the development of a secondary tumour in a distant location from the primary tumour. Malignant tumours can metastasise by either spreading into the lymph channels or blood vessels. Lymphatic spread is more typical in carcinomas, such as breast cancer, whereas haematogenous spread is more common for sarcomas (Porth, 2011). Once in the initial lymph node (known as the sentinel node) the cells may die, lay dormant or grow into a discernible mass and gain access to blood vasculature by spreading from more distant lymph nodes or through tumour-associated blood vessels infiltrating the tumour (Tobler and Detmar, 2006). Metastatic breast cancer is largely incurable and along with complications from recurrence, accounts for a large majority of breast cancer-related deaths (O'Shaughnessy, 2005). Despite advances in cancer treatment, approximately 30% of women diagnosed with earlier stage primary breast cancer eventually develop recurrent advanced or metastatic disease (O'Shaughnessy, 2005).

Evidence suggests that breast cancer stem cells play a major role in breast cancer growth and metastases. The origin of breast cancer stem cells is unknown, but may result in the transformation of normal stem/progenitor cells (Petersen and Polyak, 2010). Stem/progenitor cells are likely candidates for the origin of tumour cells (i.e. the origin of the first mutational event) due to their long lifespan, which makes them more susceptible to the accumulation of DNA mutations, and their capacity to replicate and produce multiple progeny (Takebe and Ivy, 2010). For

example, BRCA1 expression is required for the differentiation of ER stem/progenitor cells into ER-positive luminal cells, and mutations in BRCA1 resulting in the loss of DNA repair may contribute to the accumulation of genetically unstable breast stem cells, which may lead to carcinogenesis and cancer stem cell development (Liu et al., 2008).

Furthermore, genetic programmes operative in stem cells during embryonic development may become operant in cancer stem cells, and provide a mechanism for metastasis. The epithelial cell to mesenchymal cell (a type of connective tissue stem cell that can differentiate into bone, fat, cartilage, tendon and muscle cells) transition is a process seen in embryogenesis that guides the transformation of a non-mobile epithelial-like cell into mesenchymal-like cell, which is more mobile and can travel distant anatomical sites within the developing embryo (Takebe et al., 2011). Upon arrival at this distant site the epithelial-to-mesenchymal transition is reversed and the mesenchymal-like cell regains its epithelial phenotype. This process has been observed during tumour formation and may lead to metastasis, where migratory cancer cells become anchored at distant sites and then lose their migratory potential and begin to accumulate at this new site (Takebe et al., 2011).

In breast cancer, the functional loss of E-cadherin, a protein categorized as a tumour suppressor, is critical to the progression towards metastasis. E-cadherin is responsible for the formation of intracellular junctions and is involved in the downregulation of epithelial-to-mesenchymal transition in epithelial tumours (Rodriguez et al., 2012). Without E-cadherin previously stationary tumour cells are free to dislodge from their original location and become more mobile. Among other mechanisms, hypermethylation and silencing of the E-cadherin promoter is known to cause downregulation of the E-cadherin gene, CDH1, and has been associated

with the initiation of epithelial-to-mesenchymal transition and metastasis (Lombaerts et al., 2006; Graff et al., 1995).

2.4 Genetic risk factors for familial breast cancer

Assuming that most cancers develop from a single cell, and at least two mutational events are required, the findings of Knudson (1971) predicted that all cancers can be classified as either a) inherited or familial cancers caused by genetic factors, or b) sporadic cancers, those arising as a result of chance and caused by a combination of genetic and environmental factors. Both categories involve the same genetic mutations, but differ in the timing of the mutation's occurrence. For familial cancers, individuals are born with the first mutation and this mutation is carried in all of the cells in their body, while the second mutation is acquired after birth in a relevant somatic cell of these individuals. By contrast, in the case of sporadic cancers individuals acquire both mutations in somatic cells after birth. Therefore, the chances of two independent mutations occurring in the same somatic cell during the lifetime of an individual (sporadic) are significantly lower than a single mutation occurring in a somatic cell with a pre-existing mutation (familial) (Knudson, 1971). This "multiple hit" model predicts that those born with a pre-existing cancer inducing mutation are at a higher risk of developing cancer and that familial cancer will occur at younger ages and at multiple sites, while sporadic cancers will occur in older adults and in single sites (Slijepčević, 2007).

About 15 to 20% of all cases of breast cancer are thought to be familial, that is breast cancer characterized by a clear family history of disease (i.e. a mother, father, sister, brother, daughter or son who have had breast cancer) (Jacobi, 2003). The overall RR of breast cancer in a woman with a positive family history is 1.7, and the risk increases threefold if onset of the disease in a first-degree relative

was premenopausal (RR=9 if bilateral and premenopausal) compared to an RR of 1.5 in the case of a postmenopausal diagnosis (Jardines et al., 2013). Apart from a significantly younger age at time of diagnosis and a higher frequency of bilateral disease, there are no other obvious differences that affect the clinical and pathological presentation of familial and sporadic breast cancer (Slijepčević, 2007). Thus, the same genetic mutations occur in both and the underlying molecular mechanism should be the same, leading to similar clinical and pathological presentation.

The heritable component of the disease was first indicated by researchers who noticed that some breast cancers tend to cluster in families (i.e. multiple first-degree relatives were affected) (van der Groep et al., 2011). Since the early 1990's, researchers have searched for mutations in genes that could explain familial breast cancer cases (Narod and Foukes, 2004). Genes in which mutations influence the risk of breast cancer have been described based on their penetrance. Penetrance is a measure of the probability of a gene or genetic trait (phenotype) being expressed and is based on the proportion of individuals with a mutation causing a particular disorder who exhibit clinical symptoms of that disorder (Griffiths et al., 2000). Highly penetrant genes will almost always cause symptoms irrespective of the environmental effects, while, low penetrance genes produce symptoms only some of the time and can be affected by environmental factors (Slijepčević, 2007).

Ripperger and colleagues (2009) categorised breast cancer susceptibility genes and single nucleotide polymorphisms (SNPs) into three groups. These groups are a) rare high penetrance genes, which are rare mutations that confer a high risk of developing cancer, b) rare moderate-penetrance breast cancer susceptibility

genes, which are uncommon mutations in genes conferring a moderate increases in risk, and c), common low-penetrance breast cancer susceptibility SNPs, which confer only slight risk alterations but are frequently expressed in the population.

Mutations in rare high penetrance genes were the first to be discovered. In the early 1990's, genetic analyses of multiple breast cancer families revealed a common gene located on chromosome 17q that was mutated in some but not all families (Hall et al., 1990). This gene was named BRCA1 (Miki et al., 1994). Soon after, a second breast cancer predisposing gene was identified and named BRCA2 (Wooster et al., 1995). Overall, it has been estimated that inherited BRCA1 and BRCA2 mutations account for 20-40% of familial breast cancer but 5-10% of breast cancer overall (Ripperger et al., 2009). Women who inherit a BRCA1/2 mutations have a 40-65% lifetime risk of breast cancer compared to a 12% lifetime risk of women in the general population (Chen and Parmigiani, 2007; Antoniou et al., 2003), with a typically younger age of onset compared with sporadic cases of breast cancer (Hilgart et al., 2012). Mutation carriers are also susceptible to cancers of the ovary, prostate, pancreas and male breast (Venkitaraman, 2001). The prevalence of BRCA1 or BRCA2 mutations varies considerably among ethnic groups and geographical areas, with population-specific mutations and recurrent mutations described among Ashkenazi Jews and in Iceland, Netherlands, Sweden, Norway, Germany, France, Spain, Canada and countries of eastern and southern Europe (Balmana et al., 2010).

BRCA1 and BRCA2 are genes involved in DNA damage response (Gasser and Raulet, 2006). This response is activated when cells or organisms are exposed to genotoxic stress (Deng, 2006). Cellular mechanisms typically recognise DNA damage, signal the presence of DNA damage to other relevant molecules, and

activate cell cycle checkpoints and the recruitment of the machinery of DNA repair (Venkitaraman, 2001). Failure to activate these checkpoints of DNA repair following DNA damage increase the DNA's sensitivity to genotoxic agents. BRCA proteins are involved in a multitude of pivotal cellular processes. As well as contributing to DNA repair, specifically DNA double-strand breaks, and transcriptional regulation in response to DNA damage, BRCA proteins may be required for maintenance of chromosomal stability, thereby protecting the genome (i.e. the entirety of an organism's hereditary information) from damage (Venkitaraman, 2001). In addition, BRCAs transcriptionally regulate some genes involved in DNA repair, the cell cycle and apoptosis, mediated by a large number of cellular proteins that interact with BRCAs (Yoshida and Miki, 2004).

In addition to BRCA 1 and 2, other rare high penetrance genes include mutations in p53 gene, which cause the Li–Fraumeni syndrome, serine/threonne protein kinase 11 (STK11) causing Peutz–Jeghers syndrome, phosphatase and tensin homologue (PTEN) causing Cowden syndrome, neurofibromin (NF1) causing Neurofibromatosis type 1, nibrin (NBN) causing Nijmegen breakage syndrome, and mutations in cadherin 1 (CDH1) (Ripperger et al., 2009). Although these mutations are uncommon causes of breast cancer they may be highly penetrant.

However, high penetrance genes mutations account for only approximately 16-25% of familial breast cancer cases, and a mutation in the gene which causes a potentially high risk of cancer does not necessarily mean cancer will develop, therefore, interactions with other genes and environmental factors may influence disease development (Beggs and Hodgson, 2009; Rahman and Stratton, 1998). Numerous studies have failed to identify another highly penetrant BRCA gene, but have instead identified several low penetrance genes involved in familial breast

cancer (Beggs and Hodgson, 2009). High penetrance genes, such as BRCA 1/2, affect many family members and greatly increases breast cancer risk, whereas low penetrance genes do not affect as many family members and they confer a lower risk (Slijepčević, 2007).

The discoveries of lower penetrance genes indicates that inherited breast cancer susceptibility is due to a number of genetic factors, and it may well be that non-BRCA1 and BRCA2 familial breast cancer cases are due to a combination of the effects of lower penetrance gene mutations and environmental factors (Beggs and Hodgson, 2009). Ripperger and colleagues (2009) categorised these lower penetrance genes as rare, moderate-penetrance breast cancer susceptibility genes. This category consists of mutations in genes involved in the same DNA repair pathway that can cause an increased risk of breast cancer (Odds Ratio, OR=2-4), and includes ATM, checkpoint kinase 2 (CHEK2), partner and localizer of BRCA2 (PALB2), and BRCA1 interacting protein C-terminal helicase 1 (BRIP1) (Ripperger et al., 2009). In addition, RAD50 homologue, which has a role in DNA repair, telomere integrity and meiosis (i.e. cell division leading to gamete cells), may be linked with an increased breast cancer risk, but this is still being debated (Beggs and Hodgson, 2009).

The final category presented by Ripperger and colleagues (2009) is common low-penetrance breast cancer susceptibility SNPs. Each individual's DNA sequence is identical apart from 0.01% (or 1 in 1200 DNA bases). The DNA bases, at specific genomic locations, that differ between individuals are called SNPs. SNPs constitute by far the greatest type of genetic variation, and the total number of common SNPs in the human genome has been estimated to be at least 10 million (Slijepčević, 2007). Although there are studies providing contradictory evidence of

the importance of the role of SNPs, there is good evidence now that there are up to seven SNPs that have been reproducibly found to influence breast cancer risk (Beggs and Hodgson, 2009). Each SNP is expected to impact breast cancer risk to a minor extent. However, as most of these variants occur at high frequency in the investigated populations they can have a significant impact upon breast cancer risk. The current list of SNPs which are thought to increase breast cancer risk are fibroblast growth factor receptor type 2 (FGFR2), lymphocyte-specific protein 1 (LSP1), mitogen-activated protein kinase 1 (MAP3K1), transforming growth factor, beta 1 (TGFB1), TOX high mobility group box family member 3 (TOX3), as well as a locus on 2q3545 and 8q (Ripperger, 2009).

In summary, the evidence suggests that familial breast cancer is a polygenic disease (i.e. a disease caused by multiple genes). Based on current evidence, the greatest breast cancer risk is conferred by high penetrance genes, such as BRCA1 and BRCA2, although these mutations are rare in the general population. Rare moderate-penetrance genes confer a much lower risk, which can increase by inheriting more than one of these genes, while common low-penetrance breast cancer susceptibility SNPs have a minor impact upon risk but this risk can increase due to their high frequency in the population. However, only approximately 50% of familial cancer cases can be explained by high, moderate and low penetrance genes and SNPs, the other 50% may be caused by as yet unidentified genes (Atoum et al., 2012). Therefore, it seems likely that future research will uncover more.

2.5 Risk factors of sporadic breast cancer

For sporadic breast cancer, which represents the majority of breast cancer cases, there is no family history of breast cancer and somatic mutations in BRCA1 or

BRCA2 do not frequently occur in these breast cancer cases (Venkitaraman, 2001). This may suggest that the genetic alterations in sporadic cancers target other molecules whose functions are linked to those of BRCA1 or BRCA2, target genes other than BRCA1 and BRCA2 or that BRCA1 and BRCA2 are inactivated by mechanisms other than somatic mutation (Rahman and Stratton, 1998).

Knowledge of breast cancer risk factors might provide information about a woman's future if risk factors are associated with very large increases in risk above the "background" risk of the general populations. They are not necessarily "causes" of breast cancer. Risk factors that are extremely strongly associated with a disease can be considered as a potential screening test for that particular disease (Wald et al., 1999). A RR or of at least five between the highest and lowest quintiles of the distribution of a risk factor is necessary to be considered a strong indicator of risk of a particular disease (Wald et al., 1999). For example, because women who inherit a BRCA1/2 mutation have a breast cancer lifetime RR of 4-6.5, BRCA1/2 screening has been proposed for women. Investigations of breast cancer risk factors can help improve awareness of these factors and allow women to manage their risk were possible and necessary. Where risk factors are modifiable, women may reduce their risk of breast factor by lowering their exposures to such factors.

The increase in breast cancer risk associated with a history of *in situ* disease has been discussed earlier in this chapter. But in brief, the RR of developing intraductal proliferative lesions such as DCIS is eight to 11. Post-DCIS diagnosis, the probability of a woman being diagnosed with invasive breast cancer has been estimated at 5.3% within five years and 10.9% within 10 years. LN confers an increased rate of development of invasive carcinoma of about 1–2% per year, a

10-year risk of 7-8%, with a lifetime risk of 30–40%. Other risk factors that were beyond the remit of this review and hence, will not be discussed in this section include tobacco smoking, for which the evidence of an effect on breast cancer risk is equivocal (Gaudet et al., 2013; Slattery et al., 2008; Roddam et al., 2007; Gram et al., 2005; Terry et al., 2002) and other factors for which there is either a lack of evidence or an unclear relationship with breast cancer, such as bra wear, use of deodorants/antiperspirant, chemical pollutants and stress (NBOCC, 2009). Ionising radiation is an established breast cancer risk factor (RR=1.4 to 2.2), particularly in young girls in whom differentiation of breast tissue is not completed (Ronckers et al., 2005), but is of limited quantitative importance so will not be reviewed here. Exposure to electromagnetic fields has not been shown to be related to breast cancer (Feychting and Forssen, 2006).

The risk of developing breast cancer may be influenced by a number of factors. The risk factors associated with the highest increase in risk (RR≥5.0) includes being female, inheritance of BRAC 1/2, having first-degree relatives who have had breast cancer, previous invasive breast cancer and history of breast lesions, such as in situ carcinomas (NBOCC, 2010; Weir et al., 2007). The RR associated with breast densities above 75% compared to 5% have been just below five (Cummings et al., 2009; McCormack and dos Santos Silva, 2006). All other risk factors offer moderate or modest predictions for breast cancer risk.

High consumption of alcohol (Collaborative Group on Hormonal Factors in Breast Cancer, 2002), age over 50 years (Jardines et al., 2013; see figure 2.5), higher socio-economic status (Ferlay et al., 2010; see figure 2.6) and being Caucasian (Ferlay et al., 2010) are associated with moderate levels of risk of breast cancer (RR ~1.5 to >4). While later age at menopause (Trichopoulos et al., 2012),

nulliparity (Collaborative Group on Hormonal Factors in Breast Cancer, 2002), high intake of saturated fat (Thiebaut et al., 2007; Saadatian-Elahi et al., 2004), type II diabetes (Larsson et al., 2007; Lawlor et al., 2004), taller height (Baer et al., 2006; Lahmann et al., 2004; van Brandt et al., 2000), previous history of other cancers (Karahalios et al., 2009; Curtis et al., 2006), exposure to diethylstilboestrol in utero (Titus-Ernstoff et al., 2001), current or recent use of hormone replacement therapy (HRT) (Chlebowski et al., 2013; Collaborative Group on Hormonal Factors in Breast Cancer, 1997) and current use of oral contraceptives (OC) (Marchbanks et al., 2012; Hannaford et al., 2007) may confer a more modest risk of developing breast cancer (RR=1.1-1.5). There is also evidence that the influence of breast cancer risk factors is influenced by the heterogeneity of breast tumours (NBOCC, 2010).

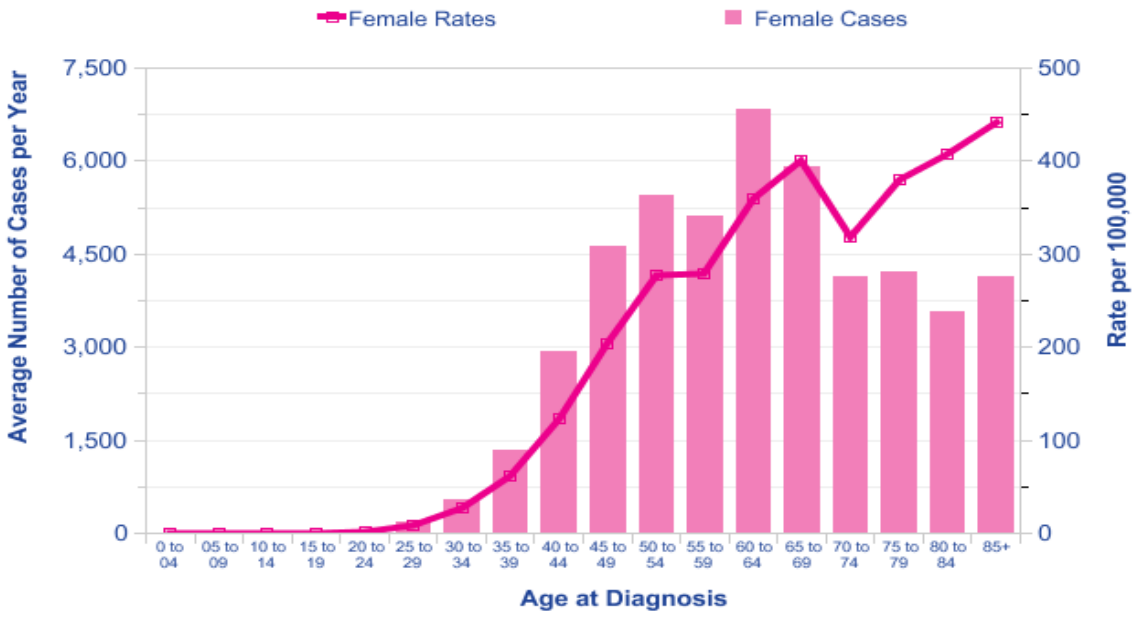


Figure 2.5 Average incidence of breast cancer per year and age-specific incidence rates, females, UK, 2008-2010 (Cancer Research UK, 2013). 80% (39,339 out of 48,975 average new cases across all ages) of new cases of female breast cancer occurred in women aged ≥50 y.

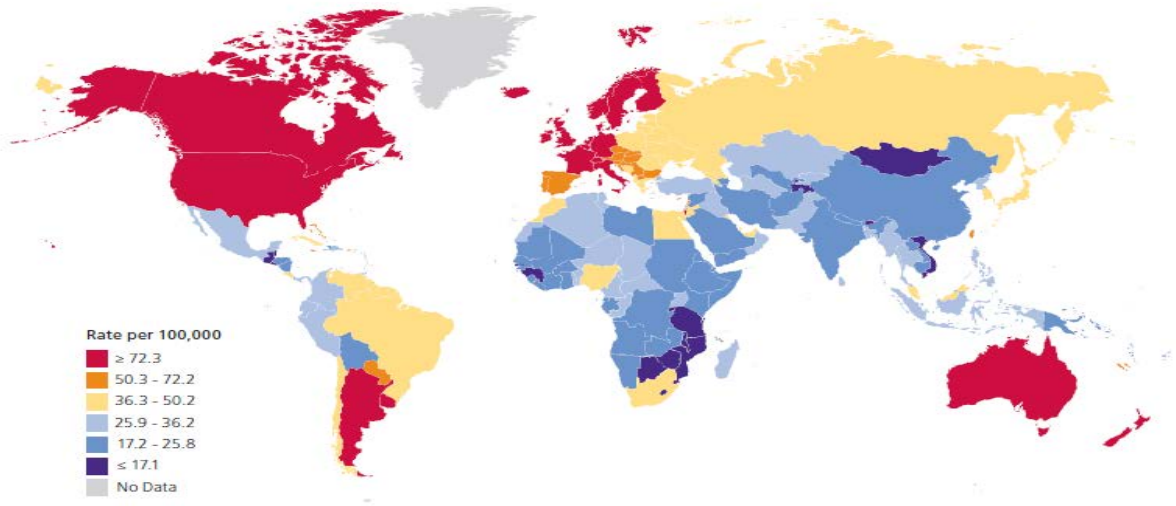


Figure 2.6. Worldwide incidences of breast cancer, countries in the red have the highest incidence while those countries in blue and purple have the lowest incidence. AS incidence rates can vary five-fold, and are highest in "developed" countries, such as USA, UK and other Western European countries and lowest in the less-developed countries, such as most African countries and parts of Asia. This variation is not fully explained by the quality and scope of screening programmes within countries (Ferlay et al., 2010)

A number of risk factors may offer modest to moderate protection against breast cancer occurrence. Parous women are at a lower breast cancer risk and each subsequent child after the first is thought to confer an additional 7% risk reduction (Weir et al., 2007). In addition, other reproductive factors such as a lower age at first birth (3% risk reduction for each one-year decrease in a woman's age at first birth) and breastfeeding of at least 12 months in duration (4.3% risk reduction for every 12 months of breastfeeding) have been associated with lower risk of breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). High vegetable intake and dietary patterns high in raw vegetables, fish and olive oil may confer a lower risk of breast cancer (Masala et al., 2012; Brennan et al., 2010; Sieri et al., 2004; Gandini et al., 2000).

Many of the risk factors outlined above are either not modifiable or modification of risk would lead to a considerable restriction in a woman's life decisions. Therefore,

there has been a focus on breast cancer risk factors that can be more readily modified. Modifiable risk factors, such as obesity and low physical activity may have only modest effects on breast cancer risk, but because of their high prevalence it has been estimated that nearly 40% of breast cancer cases could be prevented by these risk factors (Sprague et al., 2008), in addition, reducing obesity and physical inactivity can decrease risk of other chronic diseases, such as type II diabetes and CVD (Lee et al., 2012; Nocon et al., 2008; Lindstrom and Uusitupa, 2008). It is thought that the positive effects of these modifiable risk factors are mainly due to changes in endogenous hormone exposure (NBOCC, 2010; Weir et al., 2007). The next section will therefore, explore the influence of endogenous hormone exposure, overweight/obesity and physical activity on breast cancer risk.

2.5.1 Exposure to Endogenous hormones

The specific cause for the transformation of a normal breast epithelial cell into a malignant one is unknown. However, it is known that breast tissues and tumours are dependent on oestrogen for their growth. Oestrogens have been shown to promote development of breast tumours by promoting proliferation of cells with existing mutations and increasing the probability of new mutations (Key and Allen, 2002). Researchers have moved away from studying the influence of hormones indirectly through menstrual and reproductive factors, and have begun to explore the direct effects of endogenous (produced within the body) and exogenous (introduced from outside) hormones on breast cancer aetiology and pathology.

The steroid hormone group collectively known as oestrogens consist of oestradiol, oestrone and oestriol. Each oestrogen has varying levels of oestrogenic activity in the body. For premenopausal women, the secretion of oestradiol, produced from androgenic precursors (such as by androstenedione or testosterone) by the

ovaries, provides the major source of oestradiol (see figure 2.7) (Barrett et al., 2010). However, for postmenopausal women the ovaries have stopped producing oestradiol, and it is the aromatization (i.e. conversion via enzyme aromatase) of androgens (mainly dehydroepiandrosterone, DHEA, secreted by the adrenal cortex) primarily synthesised in adipose tissue to oestrone, and then to oestradiol in periphery tissues account for 90% of circulating oestradiol (Henderson et al., 1988; Santen, 1986).

Oestradiol, and the other oestrogens to a lesser degree, increase proliferation of breast epithelium and stroma, and consequently increase the possibility of mutations occurring in rapidly proliferating epithelial cells (Yaghjyan and Colditz, 2011). Oestrone is considered to have weak oestrogenic activity, but because it acts as a precursor to the more powerful oestrogen, oestradiol, for postmenopausal women it is of considerable interest to cancer researchers (Ottesen and Pedersen, 1996). Whereas most of the body's oestradiol is bound to sex-hormone binding globulin (SHBG) and subsequently unavailable for entry into cells, oestriol has a much lower affinity for binding to SHBG and as a result a greater proportion is available for biological activity (Longcope, 1984). While, increased levels of oestradiol and oesterone has been linked with an increased risk of breast cancer, oestriol, the third naturally occurring and weakest oestrogen, depending on the situation may exert either agonistic or antagonistic effects on oestrogen and may have some beneficial effects such as controlling symptoms of menopause, including hot flashes, insomnia, vaginal dryness, and frequent urinary tract infections (Head, 1998) (see figure 2.7).

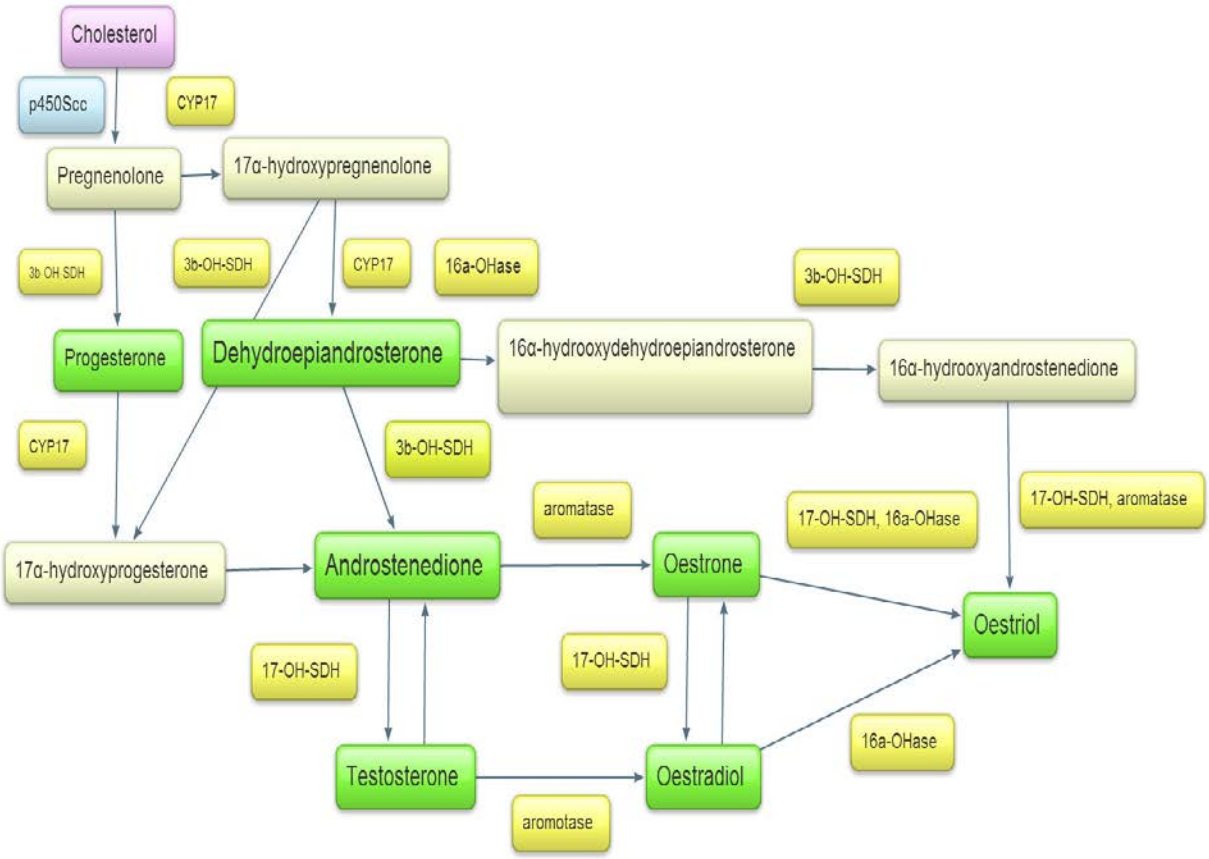


Figure 2.7 Biosynthesis of oestrogens (green boxes = sex hormones; grey boxes = sex hormone precursors; yellow boxes = enzymes) (adapted from Barrett et al., 2010; Head, 1998) (Figure abbreviations: P450scc = cytochrome P450scc, CYP11A1; CYP17 = Cytochrome P450 17α-hydroxylase/17, 20-lyase; 3b-OH–SDH = 3b-Hydroxysteroid dehydrogenase; 17-OH-SDH = 17-Hydroxysteroid dehydrogenase; 16α–OHase = 16a-Hydroxylase)

The study of hormones in relation to risk has been hampered by a number of factors, including proneness to error of laboratory analysis, the ability of clinical laboratory to reliably quantify the low circulating concentrations of oestradiol in postmenopausal women, and difficulties relating to large intra- and inter-individual fluctuations oestrogen concentrations across menstrual cycles and menstrual timing of sampling among premenopausal women (Chen, 2008; Kaaks et al., 2005). Furthermore, it is unclear whether a single sample of hormone concentrations is adequate to represent long-term exposure and whether they are influenced by samples taken post-diagnosis which may have been affected by the

disease process or its treatment (Endogenous Hormones and Breast Cancer Collaborative Group, 2002).

Possibly due in part to the problems with sampling premenopausal women mentioned above, the association between circulating oestrogen concentrations and the risk of breast cancer has been more consistent for postmenopausal women than premenopausal (Chen, 2008; Eliassen et al., 2006a; Kaaks et al., 2005; Collaborative Group on Hormonal Factors in Breast Cancer, 1997). However, a study in premenopausal women found significant increases in breast cancer risk from total and free oestradiol taken during the follicular stage but not the luteal stage of the menstrual cycle (Eliassen et al., 2006b). Moreover, there is evidence that androgens, such as testosterone and DHEA secreted by the ovaries and adrenal glands, can increase risk of breast cancer in both postmenopausal and premenopausal women (Eliassen et al., 2006; Kaaks et al., 2005).

Androgens are thought to indirectly influence breast cancer risk by conversion to oestrogens, but also directly by increasing cell proliferation (Endogenous Hormones and Breast Cancer Collaborative Group, 2002). The European prospective Investigation into Cancer and Nutrition (EPIC) study found similar increases in breast cancer risk associated with high levels of androgens in postmenopausal and premenopausal women (Kaaks et al., 2005). In a case-control study nested within the Nurses' Health Study II, the analysis of blood samples collected from 18,521 premenopausal women (including 197 cases of breast cancer) revealed that women in the highest (versus the lowest) quartiles of total and free testosterone and androstenedione had a modest increase in breast cancer risk, which was stronger for invasive breast cancer and for ER and PR-positive tumours (Eliassen et al., 2006b).

An analysis of nine prospective studies on 663 women who developed breast cancer and 1,765 women who did not (all were postmenopausal and not using HRT) found a significant increase in breast cancer risk with increased concentrations of every sex hormone examined including total oestradiol, free oestradiol, non-SHBG bound oestradiol (which comprises free and albumin-bound oestradiol), oestrone, oestrone sulphate, androstenedione, DHEA, DHEA sulphate and testosterone (Endogenous Hormones and Breast Cancer Collaborative Group, 2002). The authors (2002) found that breast cancer risk rose with increasing concentrations of sex hormones, and an approximately twofold increase in risk with both oestrogens and androgens when the highest concentrations were compared to the lowest. Higher concentrations of SHGB on the other hand was associated with a significantly lower risk of breast cancer. Subsequent studies have found similar results (Kaaks et al., 2005; Missmer et al., 2004; Zeleniuch-Jacuotte et al., 2004; Manjer et al., 2003).

Two other hormones considered as primarily female hormones, progesterone and prolactin, have been investigated in relation to the risk of breast cancer. Progesterone is a steroid hormone secreted by ovaries from the corpus luteum, the placenta and to a lesser extent the follicle, and is an important intermediate in the synthesis androstenedione, which can subsequently be converted to oestrone, and/or testosterone and oestradiol (see figure 2.7) (Barrett et al., 2010). After menopause concentrations of progesterone are extremely low because the ovaries stop secreting it. In the breast, progesterone stimulates the development of lobules and alveoli, and is hypothesized to increase cell division and thereby, lead to the accumulation of DNA damage (Chen, 2008). In support of this, it has been noted that breast cell proliferative activity is at its highest during the luteal phase of the menstrual cycle, a time when endogenous progesterone

concentrations are also high (Graham and Clarke, 1997). Prolactin is secreted by the pituitary gland and causes milk secretion from the breast after oestrogen and progesterone priming and has a role in stopping ovulation in lactating women (Barrett et al., 2010). Similar to progesterone, prolactin concentrations are much lower postmenopause. Experimental evidence suggests that prolactin can also promote cell proliferation and survival, increase cell motility, and support tumour vascularisation (Tworoger and Hankinson, 2006). However, to date, there is not enough available evidence to draw conclusions on the association between progesterone and prolactin and breast cancer risk (NBOCC, 2010).

In both prospective and retrospective studies conducted in premenopausal women, significant associations have been found between blood insulin-like growth factor (IGF)-I and breast cancer risk (Hankinson et al., 1998; Toniolo et al., 2000; Rinaldi et al., 2006; Schernhammer et al., 2006; Sugumar et al., 2004). IGF-I is a peptide growth factor, secreted by the liver, which acts as a mediator of the anabolic and mitogenic activity of human growth hormone (Loran, 2001). IGF-I signalling is vital for tumour progression because it stimulates mitogenic and metabolic activities that regulate cell proliferation, differentiation and migration, and inhibits death of normal breast epithelial cells (Rajski et al., 2010; Massoner et al., 2010). In circulation, a small amount of IGF-I is free, while the majority is bound to one of six binding proteins, which regulate IGF-I. Up to 90% of circulating IGF-I is bound to IGF-binding protein-3 (IGF-BP3) (Laron, 2001). IGF-BP3 can have tumour growth promoting and suppressing effects, it can work either IGF-I-dependently by increasing the half-life of IGF-I and modulating access to the IGF-I receptor, or IGF-I-independently by mediating their effects on target cells, where they generally have a proapoptotic affect (Canzian et al., 2010). However, evidence suggests that an increase in circulating concentrations of both IGF-I and

IGF-BP3 is associated with a moderate increase in breast cancer risk (Renehan et al., 2004; Shi et al., 2004).

A recent pooled analysis of 17 prospective studies across 12 countries, and including 4790 cases and 9428 matched controls, investigated the association between IGF-I and breast cancer risk (Endogenous Hormones and Breast Cancer Collaborative Group, 2002). The authors (2002) found that when the highest concentration of IGF-I was compared with the lowest fifth, IGF-I was associated with a 28% (95% confidence intervals, 14 to 44%) increase in breast cancer risk. This increase in risk was not modified by IGF-BPs, and did not differ by menopausal status, but seemed to be confined to ER-positive tumours.

It is possible that exposure to hormones in utero might affect future breast cancer risk, possibly due to an influence on the number or state of cells in the foetus's undeveloped breast (Colditz, 2005). A Danish study of 117,000 women followed up for an average of 28 years, examined 334 breast cancer cases and found a modest increase in breast cancer risk associated with a high birth weight and other factors that potentially indicate exposure to higher concentrations of oestrogens in utero (Ahlgren et al., 2004). Higher maternal age and higher paternal age, factors thought to increase the foetus's exposure to hormones, have also been associated with a slight increased risk of breast cancer in a recent meta-analysis (Xue and Michels, 2007). The same study (2007) also found a 50% reduction in subsequent breast cancer risk with maternal- or pre-eclampsia during pregnancy.

2.5.2 Obesity and/or overweight

Overweight and obesity are defined as the abnormal or excessive accumulation of adipose tissue (i.e. body fat) that may impair health (WHO, 2013). Anthropometric

indices, height, mass, body mass index (BMI), waist circumference, hip circumference or waist-to-hip ratio (WHR), are commonly used as tools for assessing overweight/obesity. BMI is a simple index of mass-for-height (defined as a person's mass in kilograms divided by the square of his/her height in meters, $kg \cdot m^2$) that is the most commonly method used to classify general overweight and obesity in adults (Amadou et al., 2013). The WHO (2013) defines overweight as a BMI of greater than or equal to 25 and obesity as a BMI greater than or equal to 30. Waist circumference and WHR measures used to assess abdominal obesity.

Excess bodyweight is the sixth highest contributor to the overall burden of disease worldwide (Haslam and James, 2005). It has been estimated that at least 1.1 billion adults are overweight and 312 million are obese worldwide (James et al., 2004). In England, the proportion of adults that were obese increased from 13% in 1993 to 24% in 2011 for men and from 16% to 26% for women (Health and Social Care Information Centre, 2013). The EPIC study investigated the risk of premature death associated with overweight and obesity among 359,387 participants from nine countries, follow-up on average for 9.7 years (Pischon et al., 2008). The authors (2008) found that after adjusting for educational level, smoking status, alcohol consumption, physical activity and height, a 24% (95% CI, 14 to 35%) and 94% (95% CI, 71 to 220%) increased risk of death in those with a BMI of 30.0 to $<35.0\ kg \cdot m^2$ and a BMI $\geq 35.0\ kg \cdot m^2$, respectively. In England, an estimated 34,100 deaths were attributable to obesity (6.8% of all deaths) in 2004 (Health and Social Care Information Centre, 2013). Obesity has been shown to decrease life expectancy by seven years at the age of 40 years (Peeters et al., 2003). Overweight and obesity have been associated with an increased risk of conditions including dyslipidaemia, hypertension and stroke, type II diabetes, coronary heart

disease and some cancers including endometrium, colon, kidney, oesophagus and breast (postmenopausal) (WCRF/AICR, 2007).

The relationship between body mass and BMI and breast cancer risk appears to be dependent on menopausal status. A pooled analysis of cohort studies comprising of 337,817 women and 4,385 cases of invasive breast cancer, found a significant non-linear positive correlation between BMI and the risk of breast cancer in postmenopausal women, but a significant non-linear inverse association between BMI and breast cancer risk in premenopausal women (van den Brandt et al., 2000). The same study (2000) reported a RR for postmenopausal women with BMI above 28 $kg \cdot m^2$ was 1.26 (95% CI, 1.09 to 1.46), while premenopausal women with a BMI exceeding 31 $kg \cdot m^2$ had an RR of 0.54 (95% CI, 0.34 to 0.85) compared to premenopausal women with a BMI less than 21 $kg \cdot m^2$. However, the authors (2000) did not control for physical activity in their analysis.

In a meta-analysis, the RR associated with BMI and breast cancer in postmenopausal women was 1.12 and 1.25, respectively for overweight (BMI=25-30 $kg \cdot m^2$) and obese (BMI=≥30 $kg \cdot m^2$) women (Bergstrom et al., 2001). The authors (2001) estimated a 2% increase in risk per unit increase in BMI of postmenopausal women (95% CI, 0.69 to 1.52). Similarly, an analysis of cohort studies without adjusting for mass and BMI observed a 39% lower risk of breast cancer in postmenopausal women with the smallest waist compared to the largest, and a 24% lower risk in women with the smallest WHR (Harvie et al., 2003). However, with the adjustment for BMI, the relationship between WHR and risk of postmenopausal breast cancer was abolished, but introduced an association between premenopausal breast cancer women and WHR. The implication of these findings suggest that general obesity rather than central obesity should be viewed

as a risk factor for breast cancer in postmenopausal women, whereas central obesity may be more important for premenopausal breast cancer risk.

The mechanism for the increased breast cancer risk associated with postmenopausal overweight and obesity is thought to be caused by abnormally high concentrations of free oestrogen in postmenopausal obese women (Rinaldi et al., 2006; Key et al., 2003). Because ovarian oestrogen production decreases following menopause, the rationale for high concentrations of oestrogen is attributed to the peripheral conversion of sex hormones in adipocytes (fat cells), which increase in number and size as a result of mass gain, and a fall in the concentrations of plasma SHGB (Haslam and James, 2005; Friedenreich, 2001). An alternative explanation might be that fat tissue can accumulate fat-soluble potential carcinogens, which increases their concentrations adjacent to epithelial tissue making them more available within the body (Friedenreich, 2001).

The suggested protective effect of premenopausal obesity on breast cancer risk has been attributed to excessive oestrogens and progesterone concentrations, which is proposed to interfere with the feedback regulation of the hypothalamopituitary axis, disrupt normal reproductive function and cause irregular, commonly anovulatory cycle (i.e. a cycle in which ovulation fails to occur) (Haslam and James, 2005). However, the Nurses' Health Study II found that the inverse association between obesity and breast cancer risk in premenopausal women was not explained by menstrual cycle dysfunction or ovarian disorder related infertility, suggesting that factors other than ovulation might contribute to this relationship (Michels et al., 2006).

It should be noted that although being overweight/obese is associated with a lower breast cancer risk in younger women, premenopausal breast cancer is relatively rare, and only a small proportion of premenopausal breast cancer might be avoided by being overweight/obese for younger women, while increased adiposity may confer an increased risk of the much more common postmenopausal breast cancer later in life (NBOCC, 2010). In addition, premenopausal obesity is associated with an increased risk of diabetes, heart disease and infertility and pregnancy related-problems such as pre-eclampsia, gestational diabetes, difficulties in labour and delivery, and higher rates of caesarean deliveries with more maternal and infant deaths (Haslam and James, 2005). Therefore, premenopausal weight gain should be avoided wherever possible.

In summary, postmenopausal overweight and obesity states are both strongly associated with an increased risk of developing breast cancer. Conversely, premenopausal overweight and obesity appears to confer a slight decrease in breast cancer risk. It should be noted that most of the studies in this area did not control for breast density and HRT use, which are known to influence the risk of breast cancer in postmenopausal women, and therefore, may have influenced the precision and magnitude of risk estimates.

2.5.3 Physical Activity and sedentary behaviour

Physical activity is defined as any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level, whereas exercise, a subcategory of physical activity is defined as planned, structured and repetitive and is aimed at improving or maintaining of one or more component of physical fitness (Bull and the Expert Working Groups, 2010). There is substantial evidence to support a protective role of physical activity against many of the

world's major noncommunicable diseases and a casual role for physical inactivity in the development of these diseases (WCRF/AICR, 2007). As a key determinant of energy expenditure, physical activity is fundamental to energy balance and weight control, but beyond weight control, physical activity can also reduce blood pressure, improve the level of high density lipoprotein cholesterol, and improve the control of blood glucose in overweight people and is associated with a reduced risk of colon, endometrium and postmenopausal breast cancer (WHO, 2003). Physical inactivity along with high blood pressure, high concentrations of cholesterol in the blood, inadequate intake of fruit and vegetables, overweight or obesity and tobacco use, is considered to be amongst the major causes of the world's major noncommunicable diseases, including CVD, type II diabetes and certain types of cancer, including colon, endometrium and postmenopausal breast (Lee et al., 2012; WHO, 2003). Worldwide, it is estimated that physical inactivity can be attributed to 10% (range=5·6-14·1) of the burden of disease from breast cancer (Lee et al., 2012). Furthermore, with increased industrialisation, urbanisation and mechanisation, populations become less active and become more at risk of developing breast cancer and other noncommunicable lifestyle-related diseases (WRCF/AICR, 2007).

Current physical activity guidelines for UK adults recommend daily activity, and a target of at least 150 minutes of moderate intensity activity in bouts of 10 minutes or more (e.g. 30 minutes on at least 5 days a week) over the week, or alternatively, 75 minutes of vigorous intensity activity spread across the week or a combination of moderate and vigorous intensity activity throughout a week (Bull and the Expert Working Groups, 2010). In 2008, only 39% of men and 29% of women aged 16 and over in England met the government's recommendations for physical activity, compared with 32% and 21% respectively in 1997 (Health and

Social Care Information Centre, 2013). Therefore, much of the female population are not meeting current recommended physical activity guidelines. The consequences for women regarding the risk of breast cancer can be assessed by reviewing the available epidemiological research.

An American case-control study, based on a comparison of lifetime exercise participation between 545 breast cancer cases to a similar number of women without breast cancer, estimated that women who exercised for at least 3.8 hours per week had nearly a 60% reduction in risk for breast cancer compared to women who reported no exercise participation (OR=0.42; 95% CI, 0.27 to 0.64) (Bernstein et al., 1994). Since this study, there have been many studies investigating the association between physical activity, physical inactivity and sedentary behaviour and breast cancer risk, including a number of systematic reviews.

In a systematic review based on data from 19 cohort and 29 case-control studies, Monninkhof et al. (2007) found a 20% to 80% reduction in breast cancer risk in postmenopausal women when comparing women with the highest levels of leisure-time physical activity to those with the lowest. A weak, indecisive association was found between leisure-time physical activity and breast cancer risk in premenopausal women. A dose-response relationship (i.e. greater benefits with increased physical activity) was evident in around half of the higher quality studies. The authors (2007) estimated a 6% reduction in breast cancer risk with every additional hour of physical activity assuming the level of physical activity would be sustained.

In an update of a previous review of the epidemiological evidence (Friedenreich and Cust, 2008), Lynch and colleagues (2011) reviewed 73 studies (33 cohort and

40 case-control studies) and reported that 29 studies (40% of studies) found statistically significant reductions in breast cancer risk when comparing the highest to the lowest level of physical activity. Another eight (11%) found borderline significant risk reduction for breast cancer. A decrease in the risk of breast cancer was only slightly greater among postmenopausal women (31%) than for premenopausal women (27%). The authors (2011) also reported that the greatest risk reductions were found for recreational and household activity (21%), followed by walking/cycling (18%) and occupational activity (13%). A slightly greater risk reduction was found for vigorous intensity (18%) compared to moderate intensity physical activity (15%). Risk reduction was lowest in those with a low (<22 $kg \cdot m^2$) and medium (22-25 $kg \cdot m^2$) BMI (27% and 24%, respectively) compared to those with a high (>25 $kg \cdot m^2$) or very high (>30 $kg \cdot m^2$) BMI (18% and 1%, respectively). Furthermore, there was a suggestion of a dose-response relationship between physical activity and breast cancer risk. Physical activity participation for two to three hours per week was associated with an average risk reduction of 9%, while women who reported 6.5 hours of activity per week or more had a decreased risk of 30%. The average risk reduction associated with physical activity was the same for ER-positive and ER-negative breast cancers (20%). However, average risk reductions were greater for women with ER-negative/PR-negative tumours (27%) than for women with ER-positive/PR-positive tumours (14%).

The strongest breast cancer risk reductions are observed for long-term physical activity sustained throughout life, but there is also evidence that activity performed earlier in life (including during puberty or adolescence) as well as after menopause reduces breast cancer risk (Vainio et al., 2002). Similarly, in a large cohort study, a 20% risk reduction in breast cancer was observed with long-term strenuous activity (≥5 hours per week per year) compared to inactivity (Dallal et al., 2007).

Importantly, the protective association has been noted in women of nearly every racial and ethnic background (Lynch et al, 2011).

A number of mechanisms have been proposed to explain the potential association between physical activity and breast cancer risk, including reduced exposure to oestrogen and androgens, insulin-related factors, and adipokines and inflammation (see figure 2.8 for summary). Oestrogens can inhibit apoptosis and act as mitogens in the breast, promoting the proliferation of cells through oestrogen receptor-mediated transcriptional activity and activation of cellular signalling pathways (Key et al., 2002). In postmenopausal women, production of ovarian oestrogens and adipose tissue becomes the predominant source of endogenous oestrogens. Physical activity may reduce oestrogen concentrations in postmenopausal women by facilitating a reduction in body fat. Weight loss induced by physical activity may also reduce oestrogen concentrations by lowering adipokines (a group of biologically active polypeptides produced by adipocytes or adipose tissue) concentrations, which influence oestrogen biosynthesis (Cleary and Grossman, 2009) and by lowering blood insulin concentrations, which in turn increases the concentrations of SHBG, thereby decreasing oestrogen bioavailability (Kaaks et al., 2005).

Biological mechanisms for premenopausal breast cancer:

For premenopausal women the mechanisms are less understood. However, mechanisms may be linked with delayed menarche and menstrual dysfunction, although very high levels of activity may be necessary to induce these chances (Bernstein, 2009). Alternatively, energy deficiency rather than activity levels may be a potential underlying mechanism (Loucks, 2003). Recently, a randomized controlled trial found that premenopausal women who participated in an aerobic

exercise intervention significantly increased the ratio of two key oestrogen metabolites, 2-hydroxyestrone (2OHE1) and 16α-hydroxyestrone (16αOHE1) but no other oestrogen, compared with a usual care group (Smith et al., 2013). A higher ratio would reflect a dominance of 2OHE1, which has a weak binding capacity to the ER and has been assumed to have antioestrogenic properties because of its association with normal cell differentiation and apoptosis, whereas, 16αOHE1 can bind to the ER and has been shown to induce abnormal cell proliferation (Obi et al., 2011). Therefore, exercise may positively influence the concentrations of antioestrogenic metabolites, and thereby, potentially affect breast cancer risk in premenopausal women.

Biological mechanisms for postmenopausal breast cancer:

For postmenopausal women, androgens, such as testosterone, may act to increase breast cancer risk through their conversion to oestrogens in adipose tissue, or independently of oestrogen by binding to androgen receptors to influence cell growth (Nicolas Diaz-Chico et al., 2007). Physical activity may decrease circulating androgens concentrations by decreasing adiposity or by decreasing SHBG levels by lowering insulin concentrations (Kaaks, 1996). The effect of physical activity on sex hormones may vary according to menopausal status (Schmitz et al., 2007), hormone receptor status (Adams et al., 2007) and adiposity (McTiernan et al., 2004). Evidence from randomized controlled trials consisting of physical activity interventions has shown reduced oestrogen (McTiernan et al., 2004; Friedenreich et al., 2010) and androgen concentrations (McTiernan et al., 2004; Monninkohf et al., 2009) with reduced body fat. The significant reduction in oestrogen concentration reported by Friedenreich and colleagues (2010) was still evident after adjusting for weight change, which suggests an independent role for physical activity. Observational studies support

the view that fat loss may not be necessary for changes in sex hormones (Chan et al., 2007; Verkasalo et al., 2001; Madigan et al., 1998).

Insulin may increase the potential for mutagenic events in breast cells by exerting a mitotic, anti-apoptotic effect in these cells (Lann and LeRoth, 2008). Hyperinsulinemia (excessively high blood concentrations of insulin) may increase the bioavailability of sex hormones by decreased SHBG concentrations (Kaaks, 1996). In addition, insulin-resistance and hyperinsulinemia are both related to obesity, intra-abdominal fat and adipokines and inflammatory factors, which have all been linked with an increase in breast cancer risk (Vona-Davis et al., 2007; Haslam and James, 2005; Kaaks, 1996). Therefore, it is possible that insulin may increase the risk of breast cancer independently or indirectly via biomarkers of breast cancer risk. Non-insulin dependent diabetes (or type 2 diabetes mellitus), subclinical diabetes or hyperinsulinemia with insulin resistance have all been associated with a modest increase (~20%) in the risk of breast cancer, independent of body mass (Larsson et al., 2007; Lawlor et al., 2004). Exercise in combination with weight loss can be an effective way to increase insulin sensitivity and preventing diabetes (Warburton et al., 2007; Frank et al., 2005; Ryan, 2000), and therefore, may reduce breast cancer risk.

Due to their stimulation of cell proliferation and anti-apoptosis actions, concentrations of IGFs have been considered as a potential breast cancer risk factor. Evidence from observational studies appears to suggest that an increase in circulating concentrations of both IGF-I and IGF-BP3 associates with an increase in breast cancer risk (Renehan et al., 2004; Shi et al., 2004). However, RCTs on the effects of physical activity on IGF concentrations have shown mixed results. Two trials in postmenopausal breast cancer survivors have found decreased

concentrations of IGF-I and IGF-BP3 with exercise compared with a no-exercise control (Irwin et al., 2009; Fairey et al., 2003), but another trial showed no change in IGF-I and IGF-BP3 concentrations in young women after an exercise intervention (Arikawa et al., 2010). Another recent trial observed increased serum total IGF-I and maintenance of free IGF-I concentrations in premenopausal women after weight loss induced through an energy restriction and exercise programme, suggesting that weight loss with diet and exercise does not mediate breast cancer risk through the circulating IGF-axis (Harvie et al., 2010).

The association between postmenopausal breast cancer and obesity has led to a search for the mechanisms that may explain this relationship. Obesity is characterised as a condition of chronic low-grade, systematic inflammation with elevated concentrations of inflammatory markers (Lee and Pratley, 2005). This chronic inflammatory state may promote cell proliferation, microenvironmental changes and oxidative stress which could inhibit normal cell growth and promote malignancy (Coussens and Werb, 2002). Thus, there has been considerable interest in the role of adipokines secreted by adipose tissue as a consequence of this inflammation.

Adipokines are produced in adipose tissue by adipocytes, stromal cells, which can differentiate to mature adipocytes, and macrophages, which infiltrate the adipose cell mass and are sources of the increase in local concentrations of the adipokine, tumour necrosis-α (TNF-α), observed in obese individuals (Weisberg et al., 2003). Adipokines, such as TNF-α, leptin, adiponectin, hepatocyte growth factor (HGF), heparin-binding epidermal growth factor-like growth factor (HB-EGF) and interleukin-6 (IL-6), have been implicated in the development of breast (postmenopausal) and endometrium cancer (Cymbaluk et al., 2008; Rose et al.,

2004; Harvie et al., 2003; Petridou et al., 2003). C-reactive protein (CRP) is not an adipokine, but along with TNF-α and IL-6 is considered an inflammatory marker (Lynch et al., 2011). Leptin, TNF-α, IL-6, HGF and HB-EGF, have been found to have a positive relationship with BMI, whereas, adiponectin has been shown to be negatively associated with BMI (Rose et al., 2004).

Leptin and adiponectin have received the most attention in the literature, and are thought to have opposing biological effects on breast cancer cells. Leptin may have a mitogenic effect on breast cancer cell growth, inhibit apoptosis in tumour cells and promote tumour angiogenesis, whereas, adiponectin is thought to have antimitogenic properties, enhance tumour cell apoptosis and inhibit tumour angiogenesis (Rose et al., 20004; Vona-Davis and Rose, 2007). There has been conflicting results from studies investigating the relationship between the levels of leptin in serum or plasma and breast cancer risk. Four case-control studies found an association between high serum leptin concentrations and increased breast cancer risk (Cust et al., 2009; Chen et al., 2006a; Han et al., 2005; Tessitore et al., 2000), but another six case-control studies (Woo et al., 2006; Miyoshi et al., 2006; Sauter et al., 2004; Coskun et al., 2003; Ozet et al., 2001; Petridou et al., 2000) and one case-control nested within a prospective study (Stattin et al., 2004) found no evidence of an association. Although fewer studies have investigated the relationship between adiponectin and breast cancer, each study has demonstrated an inverse association between serum adiponectin and breast cancer risk (Chen et al., 2006b; Mantzoros et al., 2004; Miyoshi et al., 2003). Miyoshi et al. (2003) found low concentrations of adiponectin were correlated with large tumours and tumours of high histological grade. Further, adiponectin may block leptin-induced production of TNF-α by macrophages (Zhao et al., 2005). In addition to leptin, HGF may increase tumour growth by facilitating angiogenesis and promotion of

cell invasion capacity. In one study, a decrease in HGF concentrations was observed after tumour removal, suggesting that HGF concentrations were related to tumour and/or excised adipose tissue (Taniguchi et al., 1995).

A recent RCT involving type II diabetics suggested that greater decreases in leptin, IL-6, TNF-α and CRP and increases in adiponectin can be achieved using high-intensity exercise rather than low-intensity and a combination of aerobic and resistance training rather than aerobic training alone (Balducci et al., 2009). In addition, a 12-month exercise intervention induced reductions in leptin in postmenopausal women and CRP in obese postmenopausal women (Campbell et al., 2009; Frank et al., 2005). Some studies have only shown decreases in adipokines with fat/weight loss (Campbell et al., 2009; Lee et al., 2009), while others have shown decreases independently of fat/weight loss (Friedenreich et al., 2011; Balducci et al., 2009; You et al., 2004). Figure 2.8 provides a summary of the potential mechanisms that may explain the role of physical activity in the reduction of breast cancer risk.

Sedentary lifestyles and breast cancer:

Sedentary lifestyles have been associated with disease-related risk factors such as central adiposity, some cancers, elevated blood glucose and insulin, diabetes and other cardiometabolic biomarkers in health adults, independent of physical activity levels (Lynch, 2010). Sedentary behaviour is defined not simply as a lack of physical activity but is a group of individual behaviours where sitting or lying is the dominant mode of posture and energy expenditure is very low. The recent Health Survey for England (Roth, 2009) reported that women over the age of 16 years engage in sedentary behaviour for an average of about five hours per day. Lynch et al. (2010) associated sedentary behavior with increased colorectal,

endometrial, ovarian and prostate cancer risk, in addition to cancer mortality in women.

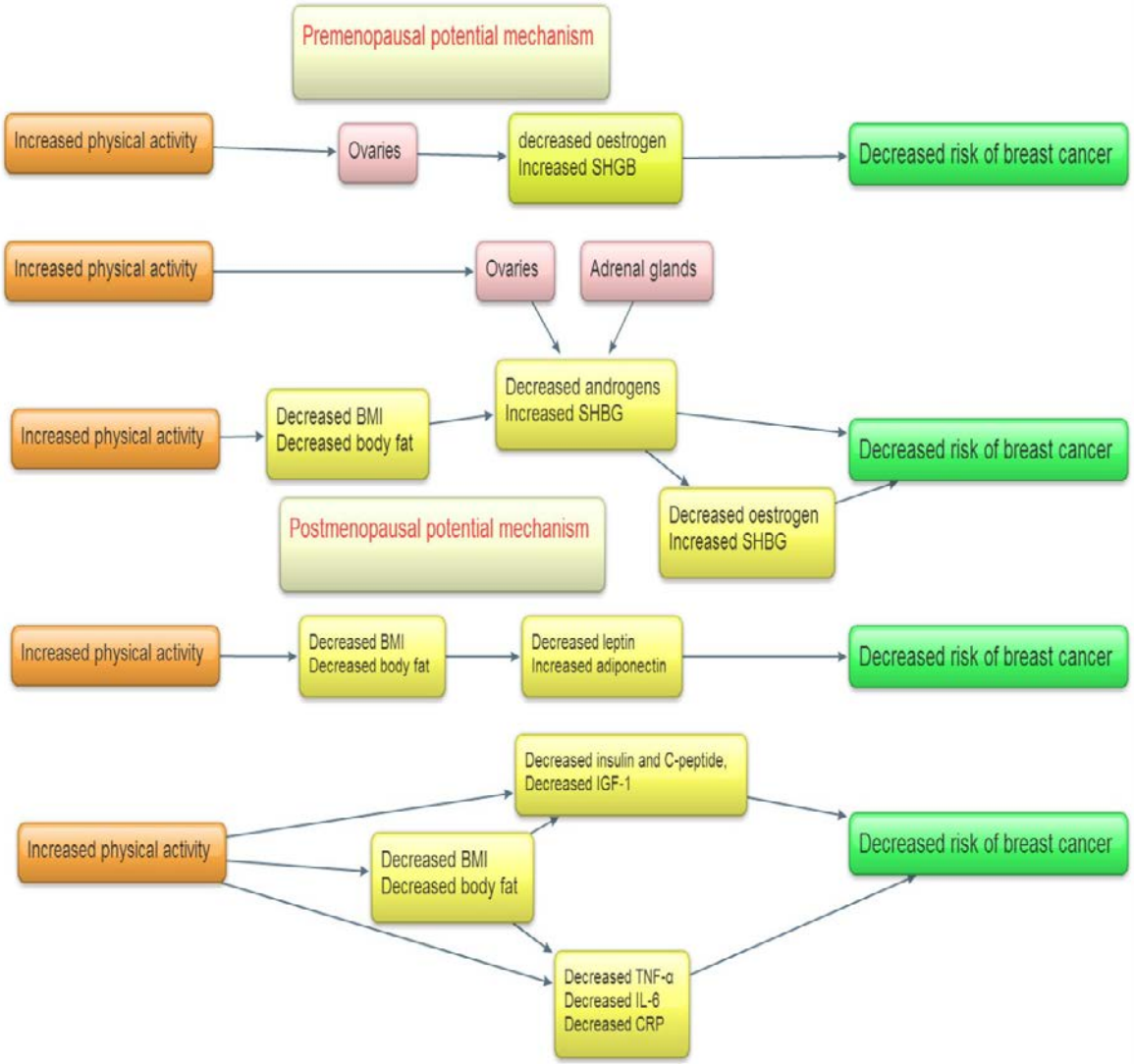


Figure 2.8 Hypothesized model of the potential mechanisms by which long-term physical activity may lower breast cancer risk in pre and postmenopausal women (adapted from Lynch et al., 2011 and Neilson et al., 2009)

In a recent, case-control study, which included 996 incident cases of breast cancer and 1,164 controls, found that sedentary behaviour was significantly associated with an increased risk of breast cancer, independent of moderate-to-vigorous activity (OR=1.81; 95% CI, 1.26 to 2.6) (Dallal et al., 2012). Similarly, a nested case-control study within a cohort study, being in the highest (>12 hours per day) versus lowest (<5.5 hours per day) quartile of total sedentary behaviour was associated with increased odds of breast cancer among white women (OR=1.94;

95% CI, 1.01 to 3.70), but not black women (OR=1.23; 95% CI, 0.82 to 1.83), after adjustment for physical activity (Cohen et al., 2013). The hypothesised mechanisms for the enhanced risk of cancer associated with sedentary behaviour are increased adiposity and metabolic dysfunction (i.e. when abnormal chemical reactions in the body disrupt normal metabolism) (Lynch, 2010).

In summary, an inverse relationship has consistently been found between increased physical activity and breast cancer risk. This association has been found in both pre- and postmenopausal women, but is strongest for postmenopausal women. Recreational and household-related physical activity appears to confer the greatest protective effect. Numerous studies have observed a dose-response relationship between physical activity and breast cancer risk. In addition, the strongest breast cancer risk reductions are observed for long-term activity sustained throughout life. It should be noted that there is considerable diversity in the measurement of physical activity in studies of physical activity and breast cancer risk, and because most studies rely on self-report to assess physical activity levels they are subject to recall bias. Nevertheless, findings have been relatively consistent across studies. The mechanisms that may explain the proposed reduction in breast cancer risk associated with physical activity include reduced exposure to oestrogen and androgens and increased concentrations of SHBG, improved insulin sensitivity and decreased concentrations of IGF-1 and adipokines and inflammatory markers, with the exception of a beneficial elevation in adiponectin concentrations. Sedentary behaviour, independently of physical activity, can increase the risk of breast cancer, possibly due to increased adiposity and metabolic dysfunction.

2.6 Treatment of breast cancer and short and long-term side effects

The treatment methods for breast cancer include surgery, chemotherapy, radiation therapy, biologic therapy and hormonal therapy. The primary treatment of operable early breast cancer is surgery with or without radiotherapy (Whelan et al., 2003). Adjuvant chemotherapy (i.e. the treatment of disease by chemical agents after the removal of the tumour) following surgery improves survival in pre- and post-menopausal women with early breast cancer (Early Breast Cancer Trialists' Collaborative Group, EBCTCG, 2005).

Most breast cancer patients have surgery to remove the breast tumour and for some the lymph nodes under the arm are extracted and investigated for the presence of cancer cells. There has been a major shift towards breast conservation surgery (i.e. surgery to remove the cancer but not the breast itself) in the last 30 years (Aebi et al., 2011). Breast-conserving surgery includes lumpectomy, which is surgery to remove the tumour and a small amount of normal tissue around it, partial mastectomy, which is surgery to remove the part of the breast that has cancer and some normal tissue around it, and segmental mastectomy, which is the removal of the lining over the chest muscles below the cancer in addition to a partial mastectomy (NCI, 2013a). A radical mastectomy, which is the surgical removal of the entire breast, underlying muscles and all axillary lymph nodes, is rarely used as a primary surgery unless the cancer is advanced at the time of diagnosis (Porth, 2011). In some instances a modified radical mastectomy, which is surgery to remove the whole breast that has cancer, many of the lymph nodes under the arm, the lining over the chest muscles and occasionally part of the chest wall muscles, may be preferred to a radical mastectomy (NCI, 2013a). A sentinel lymph node (i.e. first lymph node or nodes to which cancer cells are most likely to spread) biopsy of the affected breast is

performed during surgery to determine whether the cancer has spread to the lymph nodes. If the lymph node status is positive (i.e. cancer cells are detected) then more nodes are removed and more aggressive post-surgery treatment is required, while if negative further lymph node evaluation may not be needed.

Although the aim of breast surgery is the removal of detected breast cancer cells, undetected deposits of disease may still remain post-surgery either locally (i.e. in the residual breast tissue, scar area, chest wall or regional lymph nodes) or at distant sites that could, if untreated, develop into life-threatening recurrence (EBCTCG, 2005). Radiation therapy can be used either preoperatively or postoperatively, and is used either alone as a primary treatment method, with chemotherapy or with chemotherapy and surgery (Porth, 2011). In addition, it can be used as a palliative treatment to reduce symptoms in patients with advanced cancer. For example, it can reduce the pain associated with bone metastasis and can shrink the size of tumours which have spread to the brain from other parts of the body (NCI, 2010). Radiation therapy exerts its influence through ionising radiation produced by high energy x-rays or gamma rays. The two types of radiation therapy are external radiation, which uses a machine outside the body to send radiation towards to cancer, and internal radiation, which uses a radioactive substance sealed within needles, seeds, wires or catheters that are placed directly into or near the site of the cancer (NCI, 2013b). Whole-breast radiation therapy of between five and seven weeks duration is considered as the standard treatment following breast-conserving surgery (Lin and Tripuraneni, 2011). The method of radiation therapy used is dependent on the type and stage of the cancer being treated.

Radiation therapy can kill cancer cells by causing DNA damage directly or by indirectly causing cellular damage when the x-rays or gamma rays are absorbed into tissue, give up their energy by producing fast-moving electrons, which interact with loosely bonded or free electrons of the absorber cells to create free radicals (Porth, 2011; Lawrence et al., 2008). These free radicals interact with critical cell components and can kill cells immediately, delay or halt cell cycle progression or can cause damage to the cell nucleus resulting in apoptosis after replication. It is thought that radiation therapy is more likely to damage the rapidly proliferating and poorly differentiated tumour cells rather than the more slowly proliferating normal cells (Sharma et al., 2010). However, radiation is injurious to normal, as well as cancerous, rapidly proliferating cells and can cause both acute and chronic side effects (NCI, 2010). Acute effects of radiation therapy includes skin toxicity (i.e. pain, redness, peeling skin and oedema) in about 30% of women, which is associated with a decrease in their quality of life (Kraus-Tiefenbacher et al., 2012), and potential damage to the regions exposed to radiation such as heart, lungs, spinal cord and ribs (Hanna et al., 2013). Other side effects include fatigue and nausea with or without vomiting, while late side effects include fibrosis (formation of scar tissue), memory loss, infertility and in rare instances, a second primary cancer. The side effects that develop as a result of radiation therapy depend on the area of the body treated, the daily and total dose given, the patient's general medical condition and other treatments given at the same time.

Systemic treatment refers to the administration of chemotherapy, biologic therapy or hormonal therapy. Chemotherapy is the treatment of disease by chemical agents, and enables drugs to reach the site of the cancer as well as at distant sites. It can be used as the primary form of treatment, but is most commonly used as part of a multimodal treatment plan (Porth, 2013). Chemotherapy is

administered systemically or regionally. Systemic chemotherapy is when chemotherapy drugs are taken by mouth or injected into a vein or muscle so that the drugs can enter the bloodstream and reach cancer cells throughout the body. While, regional chemotherapy refers to chemotherapy placed directly into the cerebrospinal fluid, an organ or a body cavity, such as the abdomen, so that the drugs mainly affect cancer cells in those areas (NCI, 2013c). The way the chemotherapy is given depends on the type and stage of the cancer being treated. Chemotherapy is given in cycles of treatment days followed by days of rest. The cycles vary in length depending on the type of drug used, but typically last 14, 21 or 28 days long within a regimen of three to six months (NCI, 2013c).

Chemotherapy is designed to stop the growth of cancerous cells, either by triggering cell death or by inhibiting cell proliferation. Most chemotherapeutic drugs are more toxic to rapidly proliferating cells than to those incapable of replication or in phase G0 of the cell cycle. They are particularly effective against tumours with a high growth fraction. However, because the growth fraction of tumours is usually decreased by the time the cancer tumour is detected, treatment methods such as surgical debulking or radiation therapy, which can cause tumour cells residing in G0 to re-enter the cell cycle, are used to increase the effectiveness of chemotherapy (Porth, 2013).

In most cases, chemotherapy is most effective when combinations of more than one drug are used. During the past few decades, clinicians have moved from a combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) to anthracycline-based (e.g. doxorubicin, AdriamycinR® and epirubicin, EllenceR®) regimens, to the subsequent incorporation of taxanes (e.g. paclitaxel, Taxol® and docetaxel, Taxotere®), administration of dose-dense regimens (i.e. doses

administered over a shorter duration with less recovery between doses) and most recently, the use of biological agents (Colozza et al., 2006). Optimal administration of adjuvant chemotherapy in combination or in sequence reduces the RR for recurrence and death by more than 50%, with long-lasting benefits exceeding 15–20 years (EBCTCG, 2005). A recent Cochrane collaboration systematic review and meta-analysis found, amongst 18,304 women with operable breast cancer with 2,483 deaths, a 19% (95% CI, 12% to 25%) increase in overall survival in women administered taxane containing regimens compared to non-taxane containing regimens (Ferguson et al., 2007). Furthermore, amongst 19,943 women with 4,800 events, disease-free survival was 19% (95% CI, 14% to 27%) higher for those women administered taxane containing regimens. This finding is consistent with that of two other major meta-analyses (Qin et al., 2011; De Laurentiis et al., 2008).

Short-term effects of chemotherapy typically occur during the course of treatment and generally resolve within months of the completion of the therapy (Partridge et al., 2001). The frequency and severity of side effects are associated with the dose and type of treatment used. In general, a higher dose is associated with a higher incidence of side effects. Short-term effects of chemotherapy include nausea, emesis, alopecia, myelosuppression, stomatitis, thromboembolism, myalgias, neuropathy, cognitive dysfunction, fatigue, sore eyes, difficulty sleeping, changes in sexual functioning and reductions in HRQoL ratings (Kayl and Meyers, 2006; Partridge et al., 2001; Sitzia and Huggins, 1998). Although the short-term side effects of cytotoxic adjuvant chemotherapy are largely outweighed by its beneficial influence on breast cancer outcome and short-term patient survival, because of the increased survival rates of breast cancer patients due to both earlier diagnosis and improved chemotherapy strategies, the long-term complications of this type of

therapy has become a major issue as it could counter its effects on patient survival (Azim et al., 2011; Bovelli et al., 2010). The fact that adjuvant chemotherapy is administered to patients that may not need it has led to the consideration of the risks associated with chemotherapy versus the benefits to maximise disease-free and overall survival without compromising quality of life (Partridge et al., 2001).

The long-term effects of adjuvant chemotherapy can have a later onset and sustained impact sometimes lasting many years and in rare cases symptoms develop years after treatment (Partridge et al., 2001). These effects include cardiotoxicity, neurotoxicity, secondary leukaemia, lymphedema, premature menopause/infertility, sexual dysfunction, cognitive dysfunction and weight gain (Bovelli et al., 2010; van Dalen et al., 2010). All of these events would be expected to result in a negative impact on HRQoL long after the completion of active treatment (Mishra et al., 2012).

Biologic therapy, involving use of the drug trastuzumab (Herceptin®), is administered to stop growth of breast tumours that express HER2 receptors on their cell surface. Trastuzumab is a form of targeted therapy, which is a type of treatment that uses drugs or other substances to identify and attack specific cancer cells. The drug is a recombinant DNA derived monoclonal antibody that binds to HER2 receptor, thereby inhibiting HER2 overexpressing cancers and promoting apoptosis (Fiszman and Jasnis, 2011; Feldman et al., 2000). Amplication or overexpression results in the cancer cell gaining aggressive behavioural traits, such as enhanced growth and proliferation, increased invasive and metastatic capability and stimulation of angiogenesis (Robson and Verma, 2009). Breast cancers in which HER2 is amplified or overexpressed account for 15% of breast cancer cases, and are more likely to be poorly differentiated

tumours with a greater cell proliferation rate, positive axillary lymph node status and decreased ER and PR expression (Hortobagyi, 2005; Slamon et al., 2001). These characteristics are associated with an increased risk of disease recurrence and reduced survival (Fiszman and Jasnis, 2011; Leonard et al., 2002).

Trastuzumab is usually given by infusion following a three-weekly schedule (6 $mg \cdot kg^{-1}$), while the optimum duration of adjuvant trastuzumab is unknown, one year is usually recommended (Aebi et al., 2011). When trastuzumab is used in combination with other chemotherapeutic agents it has been found to improve the chemotherapeutic response rate (Piccart-Gebhart et al., 2005; Romond et al., 2005). Alternative types of targeted therapy used in the treatment of breast cancer include other monoclonal antibodies, such as bevacizumab (Avastin®), an antiangiogenic agent (by inhibiting actions of VEGF), tyrosine kinase inhibitors, such as lapatinib (Tykerb®), which are targeted therapy drugs that block signals needed for tumours to grow, and poly ADP-ribose polymerase (PARP) inhibitors, which are a type of targeted therapy that can block DNA repair and promote apoptosis and is being studied as a potential treatment of triple-negative breast cancer (Colozza et al., 2006).

However, Trastuzumab administration is expected to result in the development of some form of cardiac function impairment in 5% of breast cancer patients and symptomatic congestive heart failure (CHF) in 2% to 7% of patients, and increases with age over 50 years (26% for patients aged 66-70 years), borderline left ventricular ejection fraction after treatment, history of CVD and prior treatment with anthracyclines (Bartsch and Steger, 2011; Bovelli et al., 2010; Robson and Verma, 2008). Furthermore, the incidence of CHF rises to 27% when trastuzumab is used concurrently with anthracyclines plus cyclophosphamide (Bovelli et al., 2010). It is

recommended that trastuzumab use should be avoided in patients with low left ventricular ejection fraction (LVEF, <50%) and in patients whose cardiac function deteriorates during therapy (Aebi et al., 2011). However, in most cases the systolic dysfunction appears to be reversible (Guarneri et al., 2006).

In patients with ER-positive breast cancer, endocrine or hormone therapy is used to block the effects of oestrogen on the growth and proliferation of cancer cells (Porth, 2011). Hormone therapy is also used as palliative treatment for patients with hormone-sensitive metastatic disease, adjuvant treatment for women with early stage and locally advanced breast cancer, preventative measure to reduce risk of breast cancer in women at high risk, and recently, as a neoadjuvant treatment of operable and locally advanced breast cancers (Boughey et al., 2008). The two forms of hormone therapy used in breast cancer are selective oestrogen receptor modulators (SORMs) and Aromatase inhibitors (AIs).

SORMs, which include tamoxifen (Nolvadex®) and raloxifene (Evista®), are pharmacological agents that interact with the ER, and may have both oestrogen-agonistic and oestrogen-antagonistic properties based on the specific tissue target and menopausal status (Lo and Vogel, 2004). SORMs bind to ERs and block the effects of oestrogens on the growth of cancerous cells. In premenopausal patients tamoxifen alone (20 mg daily for 5 years) or the combination of ovarian function suppression or ovarian ablation (through drugs that temporarily stop the production of oestrogen by the ovaries, such as luteinizing hormone-releasing hormone agonist drugs, or oophorectomy) with tamoxifen are standard therapies particularly post-chemotherapy (Aebi et al., 2011; Bush, 2007). Raloxifene has anti-oestrogenic effects on the breast and endometrial tissue, and an oestrogenic effect on bone, lipid metabolism and blood clotting, and is used to prevent

osteoporosis and lower the risk of invasive breast cancer in postmenopausal women (Swaby et al., 2007). Unlike tamoxifen, raloxifene is not associated with an increased risk of endometrial cancer (Lo and Vogel, 2004). Although SORMs have little effect on breast cancer outcomes in ER-negative disease, for the near 80% of early breast cancer patients with ER-positive disease, treatment with tamoxifen for five years is associated with reduced local, contralateral, and distant recurrence rates and lower 15-year breast cancer mortality, with little effects on death from other causes (EBCTCG, 1988; 2005).

AIs reduce the amounts of circulating oestrogen in postmenopausal by blocking the enzyme aromatase, which converts circulating androstenedione and testosterone to oestrogen in peripheral tissues such as adipose tissue (Porth, 2011). AIs are now first-line adjuvant therapy for postmenopausal women with HR-positive disease (Boughey et al., 2008). Three AIs are currently licensed, these are anastrozole (Arimidex®), which is used instead of tamoxifen for five years, letrozole (Femara®), which is used instead of tamoxifen for five years but also for three to five years following five years of tamoxifen, and exemestane (Aromasin®), which is implemented after a woman survives disease-free for a period on tamoxifen (Hind et al., 2007). A meta-analysis by the EBCTC Group (Dowsett et al., 2010) found that the use of AIs was associated with improved disease-free survival and showed a significant but modest improvement in overall survival for postmenopausal patients who took AIs for two to three years after treatment with tamoxifen for two to three years. The authors (2010) reported no overall survival benefit in those who received AIs as initial therapy.

Hormone therapy is associated with a number of side effects dependent on the whether tamoxifen or AIs are used. Fewer hysterectomies (surgical removal of the

womb) were required in women receiving AIs (anastrozole®) when compared with those receiving tamoxifen (Howell et al., 2005). Although rare, tamoxifen has a higher risk of deep vein thrombosis, pulmonary embolus, stroke and uterine cancer than AIs (Bush et al., 2007). The most important side effects of AIs, due to near total oestrogen depletion, are decreased bone mineral density and increased fracture rates compared with tamoxifen and placebo (Boughey et al., 2008). In addition, longer duration of AI use is associated with increased odds of developing CVD in postmenopausal breast cancer patients (Amir et al., 2011). The mechanism for this is unknown, but may be due to the effects of AIs on the endothelium which may promote the development of atherosclerosis or may be due to an AI-mediated hypercholesterolemia, a well-known risk factor for development of CVD (Amir et al., 2011).

The primary importance of adjuvant therapy is to improve recurrence risk and disease-free and overall survival, while less attention has been paid to the impact of short-term side effects on HRQoL and even less on the long-term toxicity effects of treatment. Recently, with the increasing survival rates and longer life of breast cancer survivors post-treatment, more focus has been placed on the impact of treatment-induced toxicity of treatment. Particularly, given that treatment-induced toxicity may counter the survival benefits conferred by cancer treatment. Chemotherapy provides relatively moderate reductions in mortality for breast cancer patients; therefore, careful considerations of benefit and risk should be made when deciding the best course of treatment for breast cancer patients. It is also known that chemotherapy is currently given to patients who may not require such treatment. In the future, genetic profiling will hopefully lead to more targeted therapies, which will help identify patients who benefit most from chemotherapy and spare others from potentially devastating long-term adverse events and

associated reductions in HRQoL. An increasing area of research is the investigation of strategies for improving the HRQoL, disease-free survival and overall survival in breast cancer survivors. One such strategy which has been proposed for breast cancer patients is physical activity, the particular focus of this thesis. The next section will consider the evidence for the potential role of physical activity in all-cause and breast cancer-related death and recurrence.

2.7 Physical activity and risk of death and recurrence in breast cancer survivors; a systematic review and meta-analysis of epidemiological studies

2.7.1 ABSTRACT

Introduction: Strong evidence exists supporting the positive role of physical activity on breast cancer development risk. However, studies examining the effects of physical activity on clinical breast cancer outcomes including survival and prognosis have been inconclusive. Therefore, the aim of the current study was to provide a systematic review and meta-analysis of studies investigating the association between physical activity and breast cancer recurrence and death.

Methods: A comprehensive literature search identified 21 studies, of which two studies were excluded from the meta-analysis. The remaining 19 studies included 44,201 participants, 6,675 all-cause deaths and 5,485 breast cancer events (i.e. breast cancer related-deaths or recurrences).

Results: Lifetime recreational pre-diagnosis reduced all-cause death significantly by 19% but only had a borderline significant effect on breast cancer deaths. Recent (1-3 years) pre-diagnosis physical activity significantly decreased both all-case and breast cancer-related deaths (25% and 13%, respectively). Post-diagnosis physical activity reduced all-cause death by 42% and breast cancer-related deaths by 39%, and meeting recommended physical activity guidelines (i.e. ≥8 MET-h·wk^{-1}) lowered all-cause death by 38%. There were insufficient studies including recurrence as an outcome to include in the meta-analysis.

Conclusion: The current meta-analysis provides evidence for an inverse relationship between physical activity and all-cause and breast cancer-related death in breast cancer patients and supports the notion that appropriate physical activity may be an important intervention for reducing death among breast cancer survivors.

2.7.2 INTRODUCTION

Breast cancer is the most commonly diagnosed cancer and a leading cause of death from cancer in women, responsible for 23% of total cancer cases and 14% of cancer deaths worldwide (Jemal et al., 2011). In the UK, female breast cancer had the highest incidence rate of all cancers, with an average European AS rate of 124 cases per 100,000 population each year between 2007 and 2009 (ONS, 2012). Recent projections have estimated that new cases of breast cancer in England will rise by 44% from 2001 figures to 2020 (Moller et al., 2007). Breast cancer was second only to lung cancer as the cause of deaths from cancer in females (European AS mortality rate=26.1 and 31.5 per 100,000, respectively).

Risk factors associated with an increased risk of developing breast cancer are typically categorised into those which are non-modifiable, such as age and genetic predisposition, and those which are modifiable, such as alcohol consumption, overweight/obesity and physical activity. Twenty nine observational studies have found a statistically significant reduction in breast cancer risk when comparing the most physically active women to the least active (Lynch et al., 2011). A number of mechanisms have been proposed to explain the potential association between physical activity and breast cancer risk, including reduced exposure to oestrogen and androgens, insulin-related factors, adipokines and inflammation (Monninkohf et al., 2009; McTiernan et al., 2004; Key et al., 2002; Kaaks, 1996). These same mechanisms that may explain the association between physical activity and reductions in breast cancer risk, may also act to reduce the risk of premature death, breast cancer-related death and breast cancer recurrence.

Therefore, the aim of this systematic review was to evaluate the available literature pertaining to the effects of physical activity on all-cause and breast cancer-related death as well as recurrence in women diagnosed with breast cancer.

2.7.3 METHODS

A review of the epidemiologic literature on the association between physical activity and all-cause and breast cancer-related death and recurrence in women diagnosed with breast cancer was conducted using PubMed articles from 1966 up to June 2013, and a search of the reference lists of previous studies and reviews for potentially relevant additional references. The primary search strategy is presented in appendix B.

2.7.3.1 Criteria for considering studies for the review

Based on the current literature search there are at present no RCTs addressing the effects of physical activity on all-cause or breast cancer-related death or recurrence in breast cancer survivors. Therefore, a priori was given to observational studies such as cohort, case-control and cross-sectional studies for inclusion in the review. Studies were considered if they included women diagnosed with breast cancer. Studies which included cancer patients but did not provide a sub-analysis of breast cancer patients were excluded. Studies which measured and investigated the effects of either pre and/or post-diagnosis physical activity on all-cause death, breast cancer-related death and/or breast cancer recurrence were included. Only English language studies were included.

2.7.3.2 Search methods for identification of studies

All the titles and abstracts of the studies resulting from the searches of PubMed and reference lists were reviewed and articles that were clearly irrelevant were

excluded. Full-text copies of all trials were retrieved if a trial possibly or definitely met the inclusion criteria. The retrieved full-text articles were reviewed using the defined eligibility criteria, and were included if eligibility criteria was met. If there was a need for clarification of any detail of a trial, the trial authors were contacted to obtain such clarification for a complete assessment of the trial's relevance for the review to be made. Missing data were retrieved by asking study authors for the necessary data via electronic mail.

2.7.3.3 Data collection and analysis

For each trial, information on the characteristics of studies, study population, physical activity assessment and breast cancer outcomes was extracted, in addition to details of the comparisons made within each study. Characteristics of studies extracted included study design, country of origin, years patients were recruited/diagnosed with breast cancer and follow-up time. Characteristics of study population included participants' age, menopausal status, BMI, race, percentage with family history of breast cancer, percentage of participants received chemotherapy and hormonal therapy, breast cancer staging information and hormone-receptor status. Characteristics of physical activity assessment extracted included the time period between diagnosis and assessment, the period(s) of time that physical activity was assessed for, the mode of physical activity assessment and a description of the assessment tool used. In addition, information on physical activity variables and categories, comparisons made and the statistical results (hazard ratios and 95% CI) of these comparisons were extracted for the effects on all-cause death, breast cancer-related death and breast cancer recurrence. Details of any physical activity sub-analyses were also extracted from studies.

2.7.3.4 Measurement of outcome

All-cause death, breast cancer-related death and recurrence are described as time-to-event data and as such were expressed as a hazard ratio (HR) with 95% CI in all studies. The HR is a measure of relative risk over time, and in this case it is the risk of suffering death or breast cancer recurrence over a particular time period (Spruance et al., 2004). The HR is not computed at any one time point, but from all the data in the survival curve. Participants who contribute some period of time that does not end in an event (i.e. death or recurrence) are said to be "censored". In the current review, the HR provides a measure of how high the risks of these events are in one group (group 1; reference group of those who perform no/low levels of physical activity) compared to another group (group 2; those who are sufficiently physically active i.e. at least 150 min/week of moderate or 75 min/week of vigorous physical activity). A HR of greater than one would mean that the risk of an event in group two is higher than in group one. A HR of less than one would mean that the risk of an event in group two is lower than in group one, while a HR equal to one would mean that the risk of an event is approximately equal in both groups (Spruance et al., 2004). In all cases, statistical significance is assumed if the 95% CI around the HR does not include 1.0.

The HRs for all-cause death, breast cancer-related death or breast cancer recurrence of the identified studies were assessed by categorising the HR and accompanying 95% CI into the following as adopted from Lynch et al. (2011):

- Significant reductions=HR below 0.9 and upper limit 95% CI less than 1.0
- Borderline significant reductions=HR below 0.9 and upper limit 95% CI is less than 1.05
- Non-significant reductions=HR below 0.9 but upper limit 95% CI is 1.05 or above

- Null findings=HR is above or equal to 0.9 or if upper limit 95% CI is 1.05 or over

In addition to the above synthesis of data, a meta-analysis was conducted to summarise the association between higher levels of physical activity and all-cause death and breast cancer-related death. It was not possible to include recurrence data in the meta-analysis due to a lack of available data.

2.7.3.5 Meta-analysis

A meta-analysis was conducted to determine the direction and size of the possible effect that physical activity has on all-cause mortality and breast cancer-related mortality in breast cancer patients. There is conflicting results from the available data, and therefore, by combining these data the power (i.e. ability to detect a real effect as statistically significant if it exists) and precision (i.e. improve the accuracy of the effect estimate) can be improved. The comparisons were made between a) lifetime pre-diagnosis physical activity, b) recent (on average 1-3y) pre-diagnosis total physical activity and c) post-diagnosis recreational physical activity and meeting recommended physical activity guidelines post-diagnosis and all-cause and breast cancer-related death.

To date no RCTs or controlled trials address these outcomes, therefore, cohort and case-control trials were included in this meta-analysis. To perform meta-analysis of time-to-event outcomes log HR (intervention relative to control) and its standard error (SE) must be obtained. HRs and their confidence intervals were extracted from the relevant trials, and were then transformed by taking their natural logarithms (log base e, written “ln”). Standard errors (SE) were calculated from the corresponding 95% CI as follows: (ln[upper limit of CI] - ln[lower limit of

CI])/3.92 (Tierney et al., 2007). This transformation was conducted due to the asymmetry of risk ratios. The lowest value that a ratio can be is zero while the highest value is infinity. By transforming the HR to their ln the 'no effect' value becomes 0. To estimate a pooled effect and corresponding 95% CI the ln of the HRs were weighted by the inverse of their variance. For ease of interpretation the ln transformations of summary estimates and their 95% CI were converted back to their ratio (i.e. $e^{\ln(HR)}$) and presented in the results section.

Based on the ln of the HRs and the SE of the ln of the HR, the Cochran's Q test and I^2 statistics were used to assess heterogeneity among studies (Higgins et al., 2003). These statistics were used to test whether the differences obtained between studies were due to sampling error (i.e. chance). Cochran's Q test is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies (Cochran, 1954). The significance of the Q statistic was interpreted using the χ^2 distribution table. For the Q statistic, a p value of less than 0.10 was used as an indicator of the presence of heterogeneity (i.e. variation in intervention effects beyond chance), while a p-value of greater 0.10 suggests there is no significant heterogeneity (i.e. effect estimates of studies are similar). The I^2 statistic expresses the percentage of variability in effect estimate due to heterogeneity rather than chance. An I^2 value of 0% indicates no observed heterogeneity and larger values reflect increasing heterogeneity. A value greater than 50% was considered a measure of substantial heterogeneity (Higgins et al., 2003).

Study results were combined using the generic inverse-variance method. This method assigns a weight to each study based on the inverse of the variance of the effect estimate (i.e. 1 over its SE squared). In this method larger studies with

smaller SEs are given more weight than smaller studies with higher SEs, which minimises the imprecision of the pooled effect estimate (Deeks et al., 2011). A random-effects model (DerSimonian and Laird, 1986) was used to combine data where heterogeneity was suspected, while the fixed-effects model was used when heterogeneity was not suspected. The summary statistic based on either a fixed or random-effects model will be expressed as a HR and 95% CI, and not their ln for ease of comparison with other studies and consistency. The random-effects model incorporates heterogeneity among studies whereas the fixed-model ignores heterogeneity. If substantial heterogeneity is found subanalyses will be conducted when there are sufficient numbers of studies involved. These subanalyses will stratify breast cancer patients by postmenopausal status/age, BMI and ER status.

The meta-analyses and accompanying forest plots were completed using Microsoft Excel employing the method and spreadsheet described in Neyeloff et al. (2012). The main limitation of the forest plot developed by this method is that all studies are represented by squares of the same size, instead of proportional to study weight, however, study weight was provided adjacent to the plots and study weight can also be estimated by the confidence interval width. For illustration purposes effect estimates were shown on their ratio scale rather than their ln scale (see figures 2.7.1 to 2.7.7).

Funnel plots were constructed for each of the comparisons again using Microsoft Excel. Funnel plots are commonly used to assess evidence of publication bias in studies included in a meta-analysis. If smaller studies without statistically significant effects remain unpublished, this can lead to an asymmetrical appearance of the funnel plot (Harbord et al., 2009). For each funnel plot, the estimate of effect from each study (lnHR) in the meta-analysis was plotted against

a measure of its precision (SE of lnHR) (Sterne and Harbord, 2004). To facilitate the interpretation of funnel plots, we included diagonal lines (black dashed lines) representing the 95% CI around the summary treatment effect, i.e., [summary effect estimate − (1.96 × SE)] and [summary effect estimate + (1.96 × SE)] for each SE on the vertical axis (Sterne and Harbord, 2004) (see figure 2.7.7). For the purposes of displaying the centre of the plot in the absence of bias, we used the calculation of the summary ln hazard ratio (dashed red line) using fixed rather than random-effects because the random-effects estimate gives greater relative weight to smaller studies and would, therefore, be more affected if publication bias is present (Poole and Greenland, 1999). The 95% CI show the expected distribution of studies in the absence of heterogeneity or of selection biases. In the absence of heterogeneity, 95% of the studies should lie within the funnel defined by these straight lines. Because these lines are not strict 95% limits, they are referred to as “pseudo 95% confidence limits” (Sterne and Harbord, 2004).

Tests for funnel plot asymmetry, such as the Peters test (Peters et al., 2006) or the Egger regression test (Egger et al., 1997), were not used because there were fewer than 10 studies in all of the meta-analysis. The small number of studies lowers test power to a point where it is too low to distinguish chance from real asymmetry, which leads to an increase in the likelihood of a “statistically significant” result when in reality there is no association between study size and intervention effects (Sterne and Egger, 2011). Therefore, publication bias was interpreted in the context of visual inspection of funnel plots. Effect estimates from smaller studies should scatter along the bottom of the funnel plot because these studies are usually less precise (i.e. have larger SEs) and are highly subject to random variation, while the spread among larger more precise (i.e. smaller SEs) studies should narrow (Sterne et al., 2011). Thus, publication was deemed to be

absent if the funnel plot resembled a symmetrical inverted funnel shape. Publication bias was suspected if there were studies with markedly different intervention effect estimates, if smaller studies tended to lead to more or less beneficial effect estimates, and if the funnel plot was skewed and asymmetrical (i.e. gaps in bottom right and left corners indicating “missing studies”).

2.7.4 RESULTS

Through a literature search of PubMed, 1,314 potentially relevant references were identified and screened for retrieval. Based on the title and abstract 254 references were retrieved for more detailed evaluation. From the 254, 235 references were excluded as they did not meet the inclusion criteria and 21 studies were identified as appropriate for inclusion in the current review.

2.7.4.1 Results of the search

The final selection based on consensus resulted in 21 studies being included in this review (Schmidt et al., 2013; Cleveland et al., 2012; Cadmus-Bertram et al., 2011; Chen et al., 2011; George et al., 2011; Irwin et al., 2011; Emaus et al., 2010; Hellmann et al., 2010; Keegan et al., 2010; Friedenreich et al., 2009; Sternfield et al., 2009; West-Wright et al., 2009; Dal Maso et al., 2008; Irwin et al., 2008; Holick et al., 2008; Pierce et al., 2007; Abrahamson et al., 2006; Holmes et al., 2005; Borugian et al., 2004; Enger and Bernstein, 2004; Rohan et al., 1995). The above studies included 19 trials as two publications were secondary publications to two of the trials (2 publications each for the WHEL study, Cadmus-Bertram et al., 2011 and Pierce et al., 2007; and HEAL study, George et al., 2011 and Irwin et al., 2008). We reviewed and included information on trial characteristics and outcome-related data from these two secondary publications (George et al., 2011; Pierce et al., 2007). We corresponded with and requested additional data from one trial

author, and this trial author was able to provide additional data. For trial characteristics, physical activity assessment details and outcomes see the Characteristics of included studies tables 2.7.1, 2.7.2 and 2.7.3, respectively.

2.7.4.2 Characteristics of included studies

Of the 21 included studies, 19 were prospective cohort studies and two were case-control studies (Schmidt et al., 2013; Emaus et al., 2010). The total number of participants across all 21 studies was 44,201, and the mean number of participants in each study was 2,105 (*s*=1,470; range=412-4,826). The years in which participants were diagnosed with breast cancer ranged from 1974 to 2006. The mean average (mean/median) time the participants were followed-up for was 7.1 (*s*=2.0) y.

The total number of all-cause deaths observed across all studies was 6,675, and the mean number of all-cause death reported was 318 (157). Sixteen studies reported a total number of breast cancer-related deaths of 3,526 (mean±*s*=196±98). While, one study (Chen et al., 2011) combined the number of breast cancer-related deaths and breast cancer recurrences (n=450). Four studies (Sternfield et al., 2009; Irwin et al., 2008; Pierce et al., 2007; Holmes et al., 2005) reported breast cancer recurrences (total=887; mean=221.8±128.7), while one study (Friedenreich et al., 2009) reported a combined breast cancer recurrence, breast cancer progression and new primary breast cancer outcome category (n=327) and another study (Cadmus-Bertram et al., 2011) reported combined breast cancer recurrences and new primary breast cancers (n=295). Only two of these studies included breast cancer recurrences in their analyses (Sternfield et al., 2009; Holmes et al., 2005). For full details of the characteristics of included studies please see table 2.7.1.

Participant characteristics

The eligibility age of participants ranged from 18 to 80y across the 21 included studies. From the 17 studies that reported the average age of participants, the mean average age was 57 (±6) y. Other studies reported the number of participants in various age categories. Enger and Bernstein (2004) reported that 90% of participants were aged 31 to 40y, all participants in Holmes et al. (2005) were aged between 30 and 55y, and 81% and 41% of participants were aged at least 50y in Sternfield et al. (2009) and Keegan et al. (2010), respectively. Fourteen studies reported the menopausal status of participants and the average percentage of postmenopausal patients in these studies was 60 (±25) %. One study (Enger and Bernstein, 2004) consisted entirely of premenopausal women while one study (Irwin et al., 2011) comprised of only postmenopausal women.

The mean average BMI, in the 13 studies that reported this variable, was 26 (2) $kg \cdot m^2$. Other studies reported the number of participants in particular BMI categories. In these studies, the number of participants with a BMI of at least 25 kg/m^2 (i.e. overweight or obese) was 49.6% (Hellmann et al., 2010), 43% (Keegan et al., 2010), 40.7% (West-Wright et al., 2009), 56.2% (Pierce et al., 2007), 38% (Abrahamson et al., 2006), 25.4% (Enger and Bernstein, 2004) and 42% (Rohan et al., 1995). Participants in the included studies were mainly white/Caucasian/non-Hispanic white participants (number of studies, n=12, mean %=82±14.2%). Only eight studies provided the number of participants who reported a family history of breast cancer, and the average percentage of women with a family history in these studies was 16.3 (6.3) %. Nearly half of the participants in the studies had received chemotherapy (n=10, mean %=45.0±18.9%) and a similar number reported receiving hormonal therapy (chiefly tamoxifen) (n=10, mean %=45.2±18.9%).

Table 2.7.1 Characteristics of included studies

Trial (trial name), country	Sample N	Patient characteristics	Years diagnosed and follow-up duration	All-cause Death	Breast cancer death	Recurrence
Schmidt et al. (2013) (MARIE), Germany	3,393	Mean age=62.7 (IQR=58-67)y Menopausal status=NR Mean BMI=22.78 White=NR Family history=NR Chemotherapy=47.9% HT/Tamoxifen=77.5% Stage data=NR ER+/PR+=58.0% ER-/PR-=15.3%	2001-2005 in Hamburg and between 2002-2005 in the Rhein-Neckar-Karlsruhe region, Median follow-up=5.6y	367	243	330
Cleveland et al. (2012) (LIBCSP), USA	1,508	Mean age=59y Menopausal status=NR Mean BMI=26.5 Caucasian=94% Family history=20.4% Chemotherapy=NR HT/Tamoxifen=NR Stage 0=15.5% Invasive breast cancer=84.5% ER+=73.3% PR+=64.3%	1996-1997, Mean follow-up=5.6 (range=0.2-7.4)y	196	128	NR
Cadmus Bertram et al. (2011) (WHEL), USA	2,361	Mean age=53.9y Postmenopausal=80.3% Mean BMI=27.1 BMI<25.0=44.0% BMI ≥25-29.9=56.0% Non-Hispanic white=86.6% Family history=NR Chemotherapy=68.2% HT/Tamoxifen=68.3% Stage I=40.6%	1995-2000, Median follow-up=7.1 (range=1.0-10.8)y	163	NR	295*

Trial (trial name), country	Sample N	Patient characteristics	Years diagnosed and follow-up duration	All-cause Death	Breast cancer death	Recurrence
		Stage II=45.2% Stage III =14.3% HR-status=NR				
Chen et al. (2011) (SBCSS), China	4,826	Mean age=53.5 (±10)y Postmenopausal=51.1% Mean BMI=24.1 (3.4) Race=100% Chinese Family history=5.6% Chemotherapy=92.2% HT/Tamoxifen=51.9% Stage I=34.8% Stage II=51.1% Stage III=9.4% ER+=50.3% ER-=27.4%	2002-2006 Median follow-up=4.3y	436	450**	
George et al. (2011) (HEAL), USA	670[†]	Mean age =57.8y Postmenopausal=61% Mean BMI=28.0 Non-Hispanic white=57.5% Family history=NR Chemotherapy=40% HT/Tamoxifen=52% Local stage=72% Regional stage=28% ER+=67% ER-=21%	1995-1998, Median follow-up=6y	62	24	NR
Irwin et al. (2011) (WHI), USA	4,643: pre-diagnosis analysis 2,910: post-diagnosis	Mean age at enrolment=63.7y Postmenopausal=100% Mean BMI=28. Non-Hispanic whites=86% Family history=NR Chemotherapy=NR HT/Tamoxifen=NR	1993-1998, Mean follow-up=8 (±1.3)y for pre-diagnosis analysis Mean follow-up=3.3(±1.8)y for post diagnosis analysis	350: Overall 186: Post-diagnosis analysis:	194: Overall 86: Post-diagnosis analysis	NR

Trial (trial name), country	Sample N	Patient characteristics	Years diagnosed and follow-up duration	All-cause Death	Breast cancer death	Recurrence
	analysis 2,776: change analysis	Local stage=73% Regional stage=27% ER+=76% ER-=15%				
Emaus et al. (2010), Norway	1,364	Mean age=57.5 ± 8.9y Postmenopausal=61% Mean BMI=24.0±4.1 White=NR Family history=NR Chemotherapy=NR HT/Tamoxifen=NR Stage I=48.8% Stage II=41.3% Stage III=4.6% Stage IV=5.3% HR-status=NR	1975-2005, mean interval between diagnosis and end of follow-up =8.2±6.6y	429	355	NR
Hellmann et al. (2010) (CHCS), Denmark	528	Median age=67 (range=33.1-95.4)y Postmenopausal=83.9% BMI ≥25=49.6% Race=NR Family history=NR Chemotherapy=7.4% HT/Tamoxifen=7.4% Local stage=56.2% Regional=33.7% Distant=6.3% HR-status=NR	Four points of follow-up: 1976-1978, 1981-1983, 1991-1994, 2001-2003, Median follow-up=7.8 (range=0.04-29.2)y	323	178	NR
Keegan et al. (2010), (BCFR), USA, Canada and Australia	3,833	Age 40-49y=32% ≥50y=41% Menopausal-status=NR BMI<25=53% BMI 25–29.99=26%	1991-2000, Median follow-up=7.8y	623	NR	NR

Trial (trial name), country	Sample N	Patient characteristics	Years diagnosed and follow-up duration	All-cause Death	Breast cancer death	Recurrence
		BMI ≥30=17% Non-Hispanic white=75% Family history=NR Chemotherapy=49% HT/Tamoxifen=39% Stage=NR ER+=65% PR+=63%				
Friedenreich et al. (2009), Canada	1,225	Mean age at diagnosis=56 (±12.1)y Postmenopausal=62.4% Mean BMI=27.4 (±5.7) Race=NR Family history=18.4% Chemotherapy=35.6% HT/Tamoxifen=38.6% Stage 0=9% Stage I=42.3% Stage II=39.8% Stage III=8.8% HR-status=NR	1995-1997, Minimum follow-up for breast cancer recurrence and progression and new primaries=8.3y Minimum follow-up death=10.3y	341	223	327***
Sternfield et al. (2009) (LACE), USA	1,970	Mean age=61.5y Postmenopausal=67.2% Mean BMI=27.5 White=80% Family history=20% Chemotherapy=69% HT/Tamoxifen=76.2% Stage I=47.8% Stage II=49.2% Stage III=3% ER+/PR+=64.6% ER+/PR-=15.2%	1997-2000, Mean follow-up=7.2 (±1.5)y	187	102	225

Trial (trial name), country	Sample N	Patient characteristics	Years diagnosed and follow-up duration	All-cause Death	Breast cancer death	Recurrence
		ER-/PR-=17.6% ER-/PR+=2.7%				
West-Wright et al. (2009) (CTS), USA	3,539	Mean age=58.9 (±12)y Menopausal status=NR BMI<25=55.0% BMI 25-29=27.5% BMI≥30=13.2% White=89.7% Family history=NR Chemotherapy=NR HT/Tamoxifen=NR Localised stage=68.9% Regional/distant stage=30.3% ER+=72%	1995-1996 to 2004, Median follow-up =4.3y (median follow-up =3.2y and 5.3y for all-cause death and for women alive until study end, respectively)	460	221	NR
Dal Maso et al. (2008) (PACE), Italy	1,453	Age<55=47.5% Age≥55=52.5% Menopausal status=NR BMI<25=56% BMI 25-<30=32% BMI≥30=12% Caucasian=NR Family history=NR Chemotherapy=NR HT/Tamoxifen=NR Stage I=32.7% Stage II=44.2% Stage III-IV=13.3% ER+/PR+=41.5% ER+/PR-=6.3% ER-/PR-=10.1% ER-/PR+=3.6%	1991-1994, Median follow-up=12.6 (max 16.8)y	503	398	NR

Trial (trial name), country	Sample N	Patient characteristics	Years diagnosed and follow-up duration	All-cause Death	Breast cancer death	Recurrence
Holick et al. (2008) (CWLS), USA	4,482	Mean age=59 (range=20-79)y Postmenopausal=72.7% Mean BMI=25.6 Caucasian=98.7% Family history=20.4% Chemotherapy=NR HT/Tamoxifen=NR Local stage=73% Regional stage=27% HR-status=NR	1998-2001, Mean follow-up=5.5 (±1.1)y	412	109	NR
Irwin et al. (2008) (HEAL), USA	933: pre-diagnosis analysis 688: post-diagnosis PA and change in PA analysis	Mean age=55.5 (range=35-64)y Postmenopausal=60% Mean BMI=26.7 Non-Hispanic white=55.6% Family history=NR Chemotherapy=42% HT/Tamoxifen=51% Local stage=69% Regional stage=31% ER+=67%	1995-1998, Median follow-up=6 (range=5-8)y	164: Pre-diagnosis analysis 53: Post-diagnosis analysis	115: Pre-diagnosis analysis 30: Post-diagnosis analysis	56
Pierce et al. (2007) (WHEL), USA	1,490[††]	Mean age=50y Aged 40-59=69% Menopausal status=NR BMI <20=5.2% BMI 20–24.9=38.6% BMI 25–29.9=30.7% BMI ≥30.0=25.5% Race=NR Family history=NR Chemotherapy=69% HT/Tamoxifen=42% Stage I=40% Stage II=45%	1991-2000, Mean follow-up from diagnosis to censor point= 8.7y, Mean follow-up after baseline=6.7 (range=6-11)y	135	118	236

Trial (trial name), country	Sample N	Patient characteristics	Years diagnosed and follow-up duration	All-cause Death	Breast cancer death	Recurrence
		Stage III=15% ER+/PR+=61.5% ER+/PR-=10.6% ER-/PR-=20.3%				
Abrahamson et al. (2006), USA	1,264	Median age=42 (range =20-54)y Postmenopausal=22% BMI≥ 25=38% White=75% Family history=NR Chemotherapy=NR Hormone therapy (HT)/Tamoxifen=NR Local stage=57% Regional/distant stage=43% ER+=61.8% PR+=59%	1990-1992, Median follow-up=8.3 (range=3 mo-9.8)y	290	247	NR
Holmes et al. (2005) (NHS), USA	2,987	Age range=30-55y Menopausal status=NR Mean BMI=25.1 Non-Hispanic white=98% Family history=23% Chemotherapy=33.7% HT/Tamoxifen=34.7% Stage I=57.7% Stage II=35.1% Stage III=7.2% HR-status=NR	1984-1998, Median follow-up=8y	463	280	370
Borugian et al. (2004), USA	603	Mean age=55 (±11)y Postmenopausal=61% Mean BMI=26 (± 4.6) Caucasian=88% Family history=15.9% Chemotherapy=36%	1991-1992, Median follow-up=8.1y	146	112	NR

Trial (trial name), country	Sample N	Patient characteristics	Years diagnosed and follow-up duration	All-cause Death	Breast cancer death	Recurrence
		HT/Tamoxifen=43% Stage=NR ER+=76.4%				
Enger and Bernstein, (2004), USA	717	Aged 21-30y=10% Aged 31-40y=90% Premenopausal=100% BMI<20.4=24.4% BMI 20.4-24.8=50.2% BMI≥24.9=25.4% Race=NR Family history=NR Chemotherapy=NR HT/Tamoxifen=NR In-situ stage=10% Localized stage=47% Regional(distant) stage=39(4)% HR-status=NR	1983-1989, Median follow-up=10.4 (range=0.3-15.1)y	263	251	NR
Rohan et al. (1995), Australia	412	Median age=55.2y Postmenopausal=63.8% BMI≥26=42% Race=NR Family history=8.3% Chemotherapy=NR HT/Tamoxifen=NR Stage=NR ER+=54.9% ER-=28.4%	1982-1984, Median follow-up=5.5 (0.5-7.1)y	123	112	NR

Key: NR=not reported, HT=hormone treatment, HR=hormone receptor, ER=oestrogen receptor, PR=progesterone receptor, PA=physical activity
*Breast cancer recurrence and new breast cancer primaries combined
**Breast cancer-related deaths and recurrence combined
***Breast cancer recurrence and breast cancer progression and new breast cancer primaries combined
† Forms part of cohort from Irwin et al. 2008 post-diagnosis analysis
†† Consisted of some of the control group of WHEL study, see Cadmus Bertram et al. (2011) for full WHEL cohort analysis

Seventeen of the 19 studies reported stage data on the participants. However, these data were reported in different ways. Eight of the studies reported stage data in the form of the Surveillance, Epidemiology, and End Results (SEER) Program “summary staging”, which groups cancer cases into four main categories. These categories are *in situ* (abnormal cells are present only in the layer of cells in which they developed), localised (cancer is limited to the organ in which it began, without evidence of spread), regional (cancer has spread beyond the primary site to nearby lymph nodes or tissues and organs) and distant (cancer has spread from the primary site to distant tissues or organs or to distant lymph nodes) (SEER Program, 2011). In the eight studies using this method the average percentage of localised breast cancer cases was 65.5 (8.1) %. Six of the studies reported combined regional and distant cases, and the average percentage of these combined stages was 31.0 (5.6) %. While, Enger and Bernstein (2004) reported 30% regional cases and just 0.9% distant cases and Rohan et al., (1995) reported 33.7% regional and 6.3% distant cases within their respective populations. *In situ* or TNM stage 0 breast cancer cases were reported in just three studies (Cleveland et al., 2012; Friedenreich et al., 2009; Enger and Bernstein, 2004), with an average of 13 (3.5) % of this stage within these studies.

Eight studies used the TNM staging system, there were an average of 43 (8) % stage I cases, 44 (5) % stage II cases and 9 (5) % stage III cases. Only one study (Emaus et al., 2010) included separate stage IV data and reported that this stage accounted for 5.3% of the total population. Another study (Dal Maso et al., 2008) combined stage III and IV, and reported 13.3% stage III/IV breast cancers. Thirteen studies reported participant’s

tumour hormonal-status. From these studies there was an average of 66.4 (10.2) % ER-positive, 20.9 (5.6) % ER-negative, 58.9 (7.7) % PR-positive and 27.6 (7.5) % PR-negative breast cancer cases.

Physical activity assessment characteristics

All 21 studies assessed physical activity via a physical activity questionnaire. Twenty of the studies reported that these physical activity questionnaires were interview-administered. Twelve of the 21 studies reported an actual time between diagnosis of breast cancer and physical activity assessment, and there was considerable variation in this duration. The mean average time from diagnosis to assessment was 29 (39, range=2-138) months. Cadmus-Bertram et al. (2011) reported that 55% of participants completed physical activity assessments less than two years after diagnosis and the remaining 47% completed their assessment between two and four years post-diagnosis, while participants completed physical activity assessments within 12, 24 and 39 months of diagnosis in Dal Maso et al. (2008), Holmes et al. (2005) and Sternfield et al. (2009), respectively. In five studies (Cleveland et al., 2012; Hellmann et al., 2010; Friedenreich et al., 2009; West-Wright et al., 2009; Enger and Bernstein, 2004) the time between diagnosis and assessment was unclear.

Twelve of the 21 studies investigated the effects of only pre-diagnosis physical activity (Schmidt et al., 2013; Cleveland et al., 2012; Emaus et al., 2010; Hellmann et al., 2010; Keegan et al., 2010; Friedenreich et al., 2009; West-Wright et al., 2009; Dal Maso et al., 2008; Abrahamson et al., 2006; Borugian et al., 2004; Enger and Bernstein, 2004; Rohan et al., 1995), seven studies assessed only post-diagnosis physical activity

(Cadmus-Bertram et al., 2011; Chen et al., 2011; George et al., 2011; Sternfield et al., 2009; Holick et al., 2008; Pierce et al., 2007; Holmes et al., 2005) and two studies measured both pre- and post-diagnosis physical activity (Irwin et al., 2011; Irwin et al., 2008). For full details of physical activity assessment characteristics see table 2.7.2.

Characteristics of pre-diagnosis physical activity assessments

Seven of the 14 studies that included an assessment of pre-diagnosis physical activity measured lifetime physical activity (Cleveland et al., 2012; Keegan et al., 2010; Friedenreich et al., 2009; West-Wright et al., 2009; Dal Maso et al., 2008; Abrahamson et al., 2006; Enger and Bernstein, 2004). Four of these studies assessed physical activity at various age ranges. Keegan and colleagues (2010) and West-Wright et al. (2009) assessed physical activity during similar age categories (12-17, 18-24, 25-34, 35-44, 45-54, ≥55y and during 3y pre-diagnosis, and 18-24, 25-34, 35-44 and 45-54y and during 3y pre-diagnosis, respectively). While Dal Maso et al. (2008) and Abrahamson et al. (2006) both assessed lifetime physical activity in three age categories (15-19, 30-39 and 50-59y, and 12-13, 20y and year before diagnosis, respectively).

The other studies measured only physical activity that was performed for a particular frequency and/or duration over a lifetime. Schmidt et al. (2013) assessed recreational physical activity that participants performed from the age of 50y to diagnosis. Cleveland et al. (2012) measured recreational physical activity that participants had engaged in for at least one $h \cdot wk^{-1}$ for at least three months in any year over their entire lifetime, while Friedenreich and colleagues (2009) assessed occupational and household

physical activity and exercise and/or sport engaged in for at least eight, seven and two $h \cdot wk^{-1}$ for at least four months over participants entire lifetime. Enger and Bernstein (2004) asked participants about their engagement in competitive team sport or in dance or exercise classes, or jogging or running one mile at least twice weekly from menses up to breast cancer diagnosis. Borugian et al. (2004) assessed how often (per week, month or year) participants performed physical exercise, active sports, jogging or running, swimming or taking long walks, and gardening or fishing or hunting, as well as blocks walked and flights of stairs climbed on average each day pre-diagnosis. Three studies (Irwin et al., 2011; Irwin et al., 2008; Rohan et al., 1995) measured physical activity in the year prior to breast cancer diagnosis. Emaus et al. (2010) assessed leisure time physical activity on the year preceding assessment, which was on average 11.5y (range=1-29y) prior to diagnosis. It was unclear what period of time pre-diagnosis physical activity data was collected for in Hellmann et al. (2010).

All 14 of the studies that measured pre-diagnosis physical activity included recreational physical activity, while three studies (Friedenreich et al., 2009; Dal Maso; Irwin et al., 2008) also included occupational physical activity and three studies (Schmidt et al., 2013; Friedenreich et al. 2009; Borugian et al., 2004) included household physical activity. Most of the studies (Irwin et al., 2011; Keegan et al., 2010; West-Wright et al., 2009; Dal Maso et al., 2008; Irwin et al., 2008; Abrahamson et al., 2006; Borugian et al., 2004; Enger and Bernstein, 2004; Rohan et al., 1995) provided participants with a list of activities to choose from.

The physical activity variables used in these studies were considerably varied. Total lifetime recreational/leisure physical activity in MET-h·wk^{-1} units was used in three studies (Cleveland et al., 2012; Keegan et al., 2010; Friedenreich et al., 2009) and in h/wk^{-1} units in four studies (Hellmann et al., 2010; Dal Maso et al., 2008; Enger and Bernstein, 2004; Rohan et al., 1995) and in h·wk^{-1}·y^{-1} units in one study (West-Wright et al., 2009). Friedenreich et al. (2009) in addition to recreational lifetime physical activity included total lifetime, occupational and household physical activity variables in their analysis. Two studies used a recent (average 3y pre-diagnosis) physical activity variables in MET-h·wk^{-1} (Schmidt et al., 2013; Keegan et al., 2010) and one in h·wk^{-1} (West-Wright et al., 2009). While, one study (Enger and Bernstein, 2004) used average h·wk^{-1} and two studies (Irwin et al., 2011; Irwin et al., 2008) used MET-h·wk^{-1} of recreational physical activity in the year prior to diagnosis. Dal Maso et al. (2008) assessed occupational physical activity performed from age 30 to 39y as a physical activity variable. Borugian et al. (2004) included a number of physical activity variables, such as flights of stairs climbed per week, number of blocks walked per week and the frequency of sports participation, exercise, jogging, swimming and gardening per week. Finally, Emaus et al. (2010) categorised physical activity based on the time (h·wk^{-1}) spent performing leisure time physical activity (e.g. walking, cycling and exercise to keep fit).

Table 2.7.2 Physical activity (PA) assessment characteristics

Trial (name of trial)	Diagnosis to assessment time	Time period of PA assessment	Assessment mode and PA domains/items	PA variables
Schmidt et al. (2013) (MARIE)	Median=104 days after diagnosis	Pre-diagnosis recreational PA since age 50y until breast cancer diagnosis	PA was assessed using a detailed interviewer-administered questionnaire. Data collected: duration and type of occupational PA and time spent doing household tasks. A typical week was split into weekdays and weekend; the number of hours per week spent walking as well as the number of hours per week spent cycling was recorded. Participants listed up to 3 sports performed during the considered age period, including sport type, duration and frequency. MET-h·wk^{-1} were calculated by summing the average hours per week spent walking, cycling, engaged in sports or in occupation and household weighted by the appropriate MET values. Recreational PA was categorised using cutpoints: 0 (no recreational PA), <12 MET-h·week^{-1} (e.g., <2 h cycling or moderate exercise per week), 12 to <24 MET-h·wk^{-1}, 24 to <42 MET-h·wk^{-1} and ≥42 MET-h·wk^{-1})	1. Pre-diagnosis recreational PA (MET-h·week^{-1})
Cleveland et al. (2012) (LIBCSP)	"shortly after diagnosis"	Pre-diagnosis, recreational PA in which they had engaged for ≥1 h·wk^{-1} for ≥3 mo in any year over their entire lifetime.	Interview; Activity information recorded: name of activity, ages the activity was started and stopped, total years of participation in the activity, number of months per year and number of hours per week the activity was usually performed. Time periods: lifetime (h·wk^{-1} from menarche to diagnosis); premenopausal (postmenopausal women only, menarche up to menopause); onset of menopause to diagnosis, and recent PA (>10 y pre-diagnosis).	1. Total lifetime recreational PA (MET-h·wk^{-1}); 2. Moderate-intensity lifetime PA (MET-h·wk^{-1}); 3. Vigorous-intensity lifetime recreational PA (MET-h·wk^{-1})
Cadmus-Bertram et al. (2011) (WHEL)	Within 2y= 54.7% Between 2-4y= 45.3%	Post-treatment baseline (at the time of enrollment) and at 12-mo follow-up	Questionnaire; 9-item PA measure adapted from the WHI study (see Irwin et al. 2011). Assessed frequency, duration, and speed of walking outside the home and frequency and duration of participation in each of three intensities (mild, moderate, or vigorous) of exercise. Activity levels were converted into MET-h·wk^{-1} (mild PA=3, moderate PA=5, and vigorous PA=8 METs). For walking, slow, average, fast, and very fast were assessed as 2, 3, 4 and 6 METs, respectively.	1. Total PA (MET-h·wk^{-1}) 2. Mod-vig PA (MET-h·wk^{-1}) 3. Meeting PA guidelines (Yes = ≥10 MET-h·wk^{-1}; No = <10.MET-h·wk^{-1}) 4. Change in adherence to guidelines (Yes/No) 5. Change in total PA (MET-h·wk^{-1}) 6. Change mod-vig PA (MET-h·wk^{-1})

Trial (name of trial)	Diagnosis to assessment time	Time period of PA assessment	Assessment mode and PA domains/items	PA variables
Chen et al. (2011) (SBCSS)	6 mo	At baseline: 6 mo post- diagnosis, at 18-mo: preceding 12 mo (i.e. 6-mo to 18-mo), at 36-mo: preceding 18 mo (18-mo to 36-mo)	Interview; Participants asked whether they participated in exercise regularly (≥2 h·wk^{-1}) or not. If the answer was "Yes", asked to report up to 5 of the most common activities in which she participated. Frequency and duration was obtained for all exercise activities. Each activity was assigned a MET score. MET-h·wk-1 for each activity was calculated from the hours per week the participant reported engaging in that activity multiplied by the assigned MET score.	1. Exercise participation (Yes/No) 2. Exercise participation (h·wk^{-1}) 3. Exercise energy expenditure(MET-h·wk^{-1})
George et al. (2011) (HEAL)	3y (median= 30 mo)	Post-diagnosis and treatment: 2.5y post-diagnosis	For PA questionnaire detail see Irwin et al. (2008) below. Diet quality scores based on Healthy Eating Index (HEI)-2005 questionnaire	1. Recreational PA and diet quality combined
Irwin et al. (2011) (WHI)	Pre-diagnosis: mean = 4.1±2.3y Post-diagnosis: mean= 1.8±1.0y	"current walking and recreational PA" at baseline (pre-diagnosis) and years 3 and 6 (post-diagnosis)	PA questionnaire: Walking outside the home ≥10 min without stopping: Categories of frequency: 0 to 1-7 days/wk. Duration categories were <20 min, 20 to 39 min, 40 to 59 min, and 1 h or more. Four speed categories were created: <2 mph (strolling), 2-3 mph (average/normal walking), 3-4 mph (fairly fast walking), and >4 mph (very fast walking). Recreational PA: frequency of vigorous exercise ranging from never to 1 to 5+ days/wk, and session duration categories were <20 min, 20-39 min, 40-59 min or ≥1 h). Vigorous activities included aerobics, jogging, tennis, and swimming laps. Similar questions about moderate-intensity PA (e.g. biking, exercise machine, calisthenics, easy swimming, and popular or folk dancing. Converted to MET values (walking=average, 3 METs; fast, 4 METs; and very fast 4.5 METs. moderate-intensity recreational, 4 METs, and vigorous-intensity recreational, 7 METs)	1. Moderate-vigorous intensity PA (walking + recreational PA) (MET-h·wk^{-1}) 2. Moderate-intensity PA (walking + recreational PA) (MET-h·wk^{-1}) 3. Change in moderate- to vigorous-intensity PA (MET-h·wk^{-1})
Emaus et al. (2010)	Mean = 11.5±6.4y (range = 1.0–29.5y)	Pre-diagnosis recreational activity in the year preceding each survey	At inclusion, the participants indicated their usual level of PA during leisure time in the year preceding each survey, using one of 4 categories: level 1: reading, watching television, or engaging in sedentary activities; level 2: at least 4 h/wk walking, bicycling, or engaging in other types of physical activity; level 3: at least 4 h a week exercising to keep fit and participating in recreational athletics; and level 4: regular, vigorous training, or competitive sports several times a week.	1. PA categories (sedentary, moderate exercise, and regular exercise – level 3 and 4 combined)

Trial (name of trial)	Diagnosis to assessment time	Time period of PA assessment	Assessment mode and PA domains/items	PA variables
Hellmann et al. (2010) (CHCS)	Unclear	Pre-diagnosis, unclear	Self-administered questionnaire; frequency of leisure time physical activity as categorised into inactive, moderate=2-4 h·wk^{-1}, high =>4 h·wk^{-1})	1. Moderate PA of 2-4 h·wk^{-1} 2. High PA > 4 h·wk^{-1}
Keegan et al. (2010) (BCFR)	Mean= 19.2 (interquartile range = 10.6-25.2) mo	Pre-diagnosis Lifetime recreational PA at Ages 12-17y, 18-24y, 25-34y, 35-44y, 45-54y, and ≥55y, and during 3y pre-diagnosis (recent PA)	Interview-administered questionnaire: women were asked about their lifetime history of recreational PA, including moderate exercise activities or sports (i.e., brisk walking, golf, volleyball, cycling on level streets, recreational tennis or softball) and strenuous exercise activities or sports (i.e., swimming laps, aerobics, calisthenics, running, jogging, basketball, cycling on hills or racquetball). Data collected for each age interval and each type of activity (moderate and strenuous): duration of activity (0.5, 1, 1.5, 2, 3, 4-6, 7-10, ≥11 h·wk^{-1}, don't know; and 1-3, 4-6, 10-12, mo/y, don't know). H·wk^{-1} and mo per y were recoded to the midpoint (highest h·wk^{-1} interval recorded to 15) and multiplied to obtain duration of activity in h/y year for each age interval. Lifetime average h/y of PA was obtained by summing the duration of activity per y across the age intervals (except recent PA, which was considered separately), and dividing by the number of intervals. Moderate and strenuous activities were weighted by MET (5.4 for moderate PA and 8.5 for strenuous PA) and combined to obtain MET-h·wk^{-1}.	1. Lifetime PA (MET-h·wk^{-1}) 2. Recent PA (MET-h·wk^{-1})
Friedenreich et al. (2009)	Unclear	Pre-diagnosis Lifetime PA	Lifetime PA Questionnaire (Friedenreich et al., 1998); Occupational, household and recreational PA separately throughout lifetime. For frequency and duration of activities assessed number per year, months/year, weeks/ month, day/week and hours/day that each activity was performed was recorded. Activities were converted into METs.	1. Total lifetime PA (MET-h·wk^{-1}) 2. Occupational PA (MET-h·wk^{-1}) 3. Household PA (MET-h·wk^{-1}) 4. Recreational PA (MET-h·wk^{-1})
Sternfield et al. (2009) (LACE)	≤39 mo	Post-diagnosis and post-treatment, 6 mo prior to enrolment	LACE PA Questionnaire; Job/work-related PA, nonwork routine PA (household chores, caregiving, home maintenance), recreational PA and transport (motorised & active) (frequency, intensity, duration); NHS activity score using 8 activities (walking/hiking, jogging/running, bicycling, swimming, tennis, calisthenics, aerobics, squash racquetball)	1. Total PA (MET-h·wk^{-1}) 2. Mod-vig PA (MET-h·wk^{-1}) 3. H·wk^{-1} mod-intensity PA 4. H·wk^{-1} vigorous PA 5. NHS activity score (MET-h·wk^{-1})

Trial (name of trial)	Diagnosis to assessment time	Time period of PA assessment	Assessment mode and PA domains/items	PA variables
West-Wright et al. (2009) (CTS)	Unclear	Pre-diagnosis lifetime recreational PA during high school, between the ages of 18-24, 25-34, 35-44 and 45-54y, and during the past 3y (recent PA)	Information provided on recreational PA for 2 intensity levels, strenuous and moderate, at each of 6 time intervals. Long-term PA was defined for this analysis as reported activities from high school though age 54 (or the participant's age at entry if younger than 54). Recent PA was defined for this analysis as reported activity within the 3 y prior to cohort entry. Examples of strenuous exercise included running, jogging, swimming laps, racquetball, aerobics, calisthenics, and cycling on hills. Examples of moderate intensity exercise included brisk walking, golf, softball, volleyball, recreational tennis, and cycling on flat surfaces. Participants reported an average number of h·wk-1 (categories: none, 0.5, 1, 1.5, 2, 3, 4-6, 7-10, and ≥11) and the average number of mo/y (categories: 1-3, 4-5, 7-9, and 10-12) that they engaged in such activities. For each intensity level and time period, we calculated the average $h \cdot wk^{-1} \cdot y^{-1}$ by multiplying $h \cdot wk^{-1} \cdot y^{-1}$ by mo per y and dividing by 12 mo. These were summed across all eligible years and calculated the average annual $h \cdot wk^{-1}$ of long-term recreational PA for each intensity level.	1. Long-term PA combined($h \cdot wk^{-1} \cdot y^{-1}$) 2. Recent PA combined ($h \cdot wk^{-1} \cdot y^{-1}$)
Dal Maso et al. (2008) (PACE)	≤12 mo	Pre-diagnosis, at various ages over lifetime	Interview administered questionnaire: PA questions included self-reported intensity of activity at work and in leisure time separately. Both types of activity were elicited for thee specific periods of life: from 15 to 19, 30 to 39, and 50 to 59 y. For occupational PA, the scores ranged from 1 to *5,* corresponding to “very tiring,” “tiring,” “average,” “standing,” and “mainly sitting.” PA in leisure time was defined according to h·wk-1 of sport and leisure time activity such as walking, gardening, and cycling. The cutoffs were defined as <2, 2-4, 5-7, and >7 $h \cdot wk^{-1}$.	1. Occupational PA at age 30–39 y ($h \cdot wk^{-1}$) 2. Leisure time PA ($h \cdot wk^{-1}$)
Holick et al. (2008) (CWLS)	Median=5.6y	Post-diagnosis and treatment in the past year (i.e. year before enrolment)	Questionnaire modelled on NHS PA questionnaire (Holmes et al., 2005); NHS activity score in the past year average time per week spent at each of the following 8 activities (frequency, intensity duration): walking or hiking, jogging or running, bicycling, swimming laps, tennis, calisthenics, aerobics, squash or racquetball.	1. Total recreational PA (MET-$h \cdot wk^{-1}$) 2. Moderate-intensity recreational PA (MET-$h \cdot wk^{-1}$) 3. Vigorous-intensity PA (MET-$h \cdot wk^{-1}$)

Trial (name of trial)	Diagnosis to assessment time	Time period of PA assessment	Assessment mode and PA domains/items	PA variables
Irwin et al. (2008) (HEAL)	Pre-diagnosis PA: median= 5 (range= 4-8) mo Post-diagnosis: median= 2.5y	Pre-diagnosis: 1 y pre-diagnosis, Post-diagnosis and treatment: 2 y post-diagnosis	Interview-administered questionnaire: Modifiable Activity Questionnaire (Kriska, 1997) included recreational, occupational, and household PA (type, duration, and frequency). PA categorized: light (<3 MET), moderate (3-6 MET) or vigorous (>6 MET). Reported recreational PA only.	1. Recreational PA (MET-h·wk^{-1}) 2. Change in PA from pre-diagnosis to post-diagnosis (MET-h·wk^{-1})
Pierce et al. (2007) (WHEL)	Mean time from diagnosis to enrolment= 2y (maximum= 4y)	Post-diagnosis and post-treatment baseline (at the time of enrollment)	Questionnaire same as Cadmus-Bertram et al. (2011) above.	1. Total PA (MET-h·wk^{-1}) 2. Combined dietary pattern–PA lifestyle
Abrahamson et al. (2006)	Median= 4.2 mo	Pre-diagnosis, Ages 12-13 y, Age 20 y and year before diagnosis	Interview questionnaire; Frequency of vigorous activities (lap swimming, dance, basketball, gymnastics, running, fast cycling, aerobics, or field hockey). Frequency of moderate activities (brisk walking, volleyball, recreational tennis, softball, leisurely cycling, or golfing). Relative units of PA were derived from frequency/wk times MET scores for vigorous, 9 METs, and moderate, 5 METs activities.	1. Relative units of recreational PA for each time period (MET x frequency of activity)
Holmes et al. (2005) (NHS)	≥24 mo	Post-diagnosis and post-treatment, in the year before enrolment	Questionnaire; NHS activity score in the past year average time per week spent at each of the following 8 activities (frequency, intensity duration): walking or hiking, jogging or running, bicycling, swimming laps, tennis, calisthenics, aerobics, squash or racquetball	1. Total MET-h·wk^{-1} (NHS activity score)
Borugian et al. (2004)	Mean=2 mo after surgery but before adjuvant treatment	Pre-diagnosis, Unclear	Questionnaire; How often (per week, month, or year) the participant does each of the following: physical exercise, active sports, jogging or running, swimming or taking long walks, and gardening or fishing or hunting, as well as blocks walked and flights of stairs climbed on average each day.	1. Flights of stairs climbed/wk 2. Number of blocks walked/wk 3. Days sports participation/wk 4. Days exercise/wk 5. Days jogging/wk 6. Days swimming per wk 7. Days gardening /wk

Trial (name of trial)	Diagnosis to assessment time	Time period of PA assessment	Assessment mode and PA domains/items	PA variables
Enger and Bernstein, (2004)	"Interviewed after learning about diagnosis"	Pre-diagnosis, Lifetime recreational PA, up to 1-y before diagnosis	Interview; Patients asked if they had ever participated ≥2/wk on a competitive athletic team or in dance or exercise classes, or if they jogged or ran 1-mile ≥2/wk. For each activity the age started and stopped, the type and the average number of h·week^{-1} of participation was recorded. Each episode when activities were started and stopped more than once or when the amount of time spent in the activity changed was recorded. The number of h·wk^{-1} each patient participated in all recreational exercise activities beginning with the year of each woman's first menstrual period and ending at 1y pre-diagnosis date was computed.	1. Average hours of PA per week from first menses to 1-y prior to diagnosis 2. Average hours of PA per week during year before 1-y prior to diagnosis 3. H·wk-1 from first menses to 1-y prior to diagnosis
Rohan et al. (1995)	Average time from diagnosis to assessment= 4.8 mo	Pre-diagnosis, one year prior to diagnosis	Interview-administered questionnaire; Participants were asked to report how many h·wk^{-1} they spend doing light (e.g. bowls, walking, golf), moderate (e.g. dancing, horseback riding) and vigorous (e.g. competitive squash, tennis) recreational activities. H·wk^{-1} were converted to kcal/min expended (5 kcal/min for light, 7.5 kcal/min for moderate and 10 kcal/min for vigorous activities)	1. Total recreational PA (kcal/min)

Studies also analysed the effects of different physical activity intensities on breast cancer outcomes. Cleveland et al. (2012) included moderate-intensity and vigorous-intensity lifetime physical activity (MET-h·wk^{-1}) and Irwin et al. (2011) moderate-intensity and vigorous-intensity physical activity (MET-h·wk^{-1}) in the year prior to diagnosis. Abrahamson et al. (2006) used relative units (METs x frequency) of moderate-vigorous recreational physical activity for year before diagnosis and relative units averaged over age 13y, age 20y and year pre-diagnosis.

Characteristics of post-diagnosis physical activity assessments

Three of the nine studies that included post-diagnosis physical activity (Cadmus-Bertram et al., 2011; Irwin et al., 2011; Pierce et al., 2007) assessed the amount participants "currently" engage in walking outside the home for more than 10 min without stopping and recreational physical activity separated into moderate-intensity physical activities (including biking outdoors, exercise machine, calisthenics, easy swimming and popular or folk dancing) and vigorous activities (aerobics, jogging, tennis and swimming laps). Two of these studies included multiple physical activity assessment points. Cadmus-Bertram et al. (2011) assessed physical activity at baseline (within 4y of diagnosis) and at one year follow-up, while Irwin et al. (2011) measured physical activity at years three and six post-diagnosis.

Two of the studies (Holick et al., 2008; Holmes et al., 2005) assessing post-diagnosis physical activity measured the amount of leisure-time physical activity (chosen from a list of 6-8 activities) participants engaged in per week "during the past year" expressed in MET-h·wk^{-1}. The

modifiable activity questionnaire, which measures the usual amount of recreational and occupational activity performed in the past-year (reported month-by-month) and sums and divides this into an average of physical activity per week (MET-h·wk^{-1}), was used in the two studies from the HEAL trial (George et al., 2011; Irwin et al., 2008).

Sternfield et al. (2009) measured occupational, household, active transport and recreational physical activities over the six month period prior to enrolment (≤39 month's post-diagnosis). This study (2009) also included the nine-activity assessment used in the NHS trial (Holmes et al., 2005). Chen and colleagues (2011) assessed the amount of regular exercise (≥2 h·wk^{-1}) performed by participants expressed in MET-h·wk^{-1} at six months after breast cancer diagnosis (baseline), during the 12 months between baseline and 18-month assessment point and during the 18 months between the 18 and 36-month assessment points.

Similar to the studies measuring pre-diagnosis physical activity, studies assessing post-diagnosis activity included a variety of activity variables to measures their influence on breast cancer outcome. The two studies of the WHEL trial (Cadmus-Bertram et al., 2011; Pierce et al., 2007) both used a total physical activity variable expressed in MET-min·wk^{-1}, while Cadmus-Bertram et al. (2011) also included variables such as moderate-vigorous physical activity (MET-h·wk^{-1}), achieving recommended levels (≥10 MET-h·wk^{-1}) of physical activity (yes/no), change in meeting recommended levels from baseline to one year post-baseline (no change/yes to no/no to yes) and change in moderate-vigorous physical activity from baseline to one year after baseline. Irwin et al. (2011) used

the same physical activity assessment but included moderate-vigorous intensity and moderate-intensity physical activity variables expressed in MET-h·wk^{-1} variables in their analysis.

Three studies (Sternfield et al., 2009; Holick et al., 2008; Holmes et al., 2005) included a total physical activity (MET-h·wk^{-1}) variable based on the NHS recreational physical activity assessment. Holick et al. (2008) also separated total physical activity into moderate-intensity (MET-h·wk^{-1}) and vigorous-intensity (MET-h·wk^{-1}) recreational physical activity. While Sternfield et al. (2009) used total activity (MET-h·wk^{-1}), moderate-to-vigorous physical activity (MET-h·wk^{-1}) and time in moderate-intensity activities (h·wk^{-1}) variables from a separate assessment. Of the two studies from the HEAL trial, both (George et al., 2011; Irwin et al., 2008) included a total recreational physical activity (MET-h·wk^{-1}) variable in their analysis. While Chen and colleagues (2011) used the following variables to analyse the influence of exercise on breast cancer outcomes, exercise participation (yes/no), amount of exercise (h·wk^{-1}) and exercise energy expenditure expressed in MET-h·wk^{-1}.

The two studies that assessed pre- and post-diagnosis physical activity included change in moderate-vigorous intensity physical activity (MET-h·wk^{-1}) (Irwin et al., 2011) and change in recreational physical activity (MET-h·wk^{-1}) (Irwin et al., 2008). Two studies investigated the combined effects of physical activity and diet (George et al., 2011; Pierce et al., 2007), and were therefore, excluded from the analysis of study results.

2.7.4.3 Qualitative synthesis of the results of studies

Full details of results from the epidemiological studies can be found in table 2.7.3.

Lifetime physical activity and all-cause death

Statistically significant risk reductions for all-cause death in breast cancer survivors who performed the highest versus lowest level of pre-diagnosis lifetime recreational physical activity was found by two studies (Cleveland et al., 2012; West-Wright et al., 2009), borderline significant risk reductions was observed in two studies (Dal Maso et al., 2008; Friedenreich et al., 2008), a non-significant risk reduction was reported by one study (Keegan et al., 2010), while two studies reported null-findings (Emaus et al., 2010; Abrahamson et al., 2006). Only one study reported a null-finding for the association between all-cause death and the highest versus the lowest categories of pre-diagnosis total lifetime physical activity (occupational, household and recreational physical activity combined) and pre-diagnosis lifetime household physical activity (Friedenreich et al., 2008).

In regards to the role of physical activity intensity, two studies investigated the association between risk of all-cause death in breast cancer survivors who perform the highest versus the lowest amount of moderate-intensity pre-diagnosis lifetime recreational physical activity, and one study found a significant reduction in risk (Cleveland et al., 2012), while the other found a non-significant reduction in risk (Friedenreich et al., 2008). Two studies found a non-significant risk reduction in all-cause death with high versus low levels of pre-diagnosis lifetime vigorous-intensity physical activity (Cleveland et al., 2012; Friedenreich et al., 2008). Two studies observed a

null-finding for pre-diagnosis lifetime occupational physical activity and all-cause death when the highest category was compared to the lowest (Dal Maso et al., 2008; Friedenreich et al., 2008).

Lifetime pre-diagnosis physical activity and breast cancer-related death

One study found a statistically significant reduction in risk of breast cancer-related death when comparing the highest versus lowest level of pre-diagnosis lifetime recreational physical activity (Friedenreich et al., 2008), while two studies reported non-significant risk reductions (Cleveland et al., 2012; Dal Maso et al., 2008) and three reported null-findings (Emaus et al., 2010; West-Wright et al., 2009; Enger and Bernstein, 2004). Two studies observed null-findings when comparing the risk of breast cancer-related death in the highest and lowest occupational lifetime physical activity categories (Dal Maso et al., 2008; Friedenreich et al., 2008). One study reported a borderline significant reduction in risk of breast cancer-related death and the highest versus the lowest categories of pre-diagnosis total lifetime physical activity (occupational, household and recreational physical activity combined), and a null-finding for the association of highest versus the lowest pre-diagnosis lifetime household physical activity (Friedenreich et al., 2008).

Regarding physical activity intensity, one study found a statistically significant reduction in risk of breast cancer-related death when comparing breast cancer survivors who performed the highest versus lowest levels of moderate-intensity lifetime physical activity (Friedenreich et al., 2008), while another study found a non-significant risk reduction (Cleveland et al., 2012). One study reported a statistically significant risk reduction for the

highest versus the lowest amounts of lifetime vigorous-intensity (Friedenreich et al., 2008), and one study reported a non-significant risk reduction (Cleveland et al., 2012).

Recent pre-diagnosis physical activity and all-cause death

Two studies found a statistically significant risk reduction for all-cause death when comparing the highest versus lowest level of pre-diagnosis recent (1-3y prior to breast cancer diagnosis) recreational physical activity in breast cancer survivors (Schmidt et al., 2013; Irwin et al., 2011), two found a borderline significant risk reduction (Keegan et al., 2010; West-Wright et al., 2009), two found a non-significant decrease (Irwin et al., 2008; Abrahamson et al., 2006), and finally one reported a null-finding (Hellmann et al., 2010). One study found a significant risk reduction in all-cause deaths for the highest versus the lowest levels of pre-diagnosis recent moderate-intensity physical activity (Irwin et al., 2011).

Recent pre-diagnosis physical activity and breast cancer-related death

Of the studies that reported the association between recent pre-diagnosis recreational physical activity and breast cancer-related death, one study found a statistically significant reduction in risk in the highest physical activity category compared to the lowest (West-Wright et al., 2009), one observed a borderline significant risk reduction (Irwin et al., 2011), two found a non-significant risk reduction (Irwin et al., 2008; Enger and Bernstein, 2004), while the remaining four reported null-findings (Schmidt et al., 2013; Hellmann et al., 2010; Borugian et al., 2004; Rohan et al., 1995). One study reported a non-significant reduction in risk of breast cancer-related deaths for the highest versus the lowest levels of pre-

diagnosis recent moderate-intensity physical activity (Rohan et al., 1995). The only study that investigated the association between recent pre-diagnosis vigorous-intensity physical activity and breast cancer-related death reported a null-finding comparing the highest versus the lowest categories (Rohan et al., 1995).

Lifetime and recent pre-diagnosis physical activity and recurrence

One study (Friedenreich et al., 2008) reported a statistically significant reduction in breast cancer events (combined breast cancer recurrence, breast cancer progression and new breast cancer primaries) when comparing the highest versus the lowest moderate-intensity lifetime recreational physical activity, a borderline statistically significant reduction with lifetime recreational physical activity, and null-findings for total lifetime physical activity, lifetime occupational physical activity, lifetime household physical activity and lifetime vigorous-intensity physical activity. Schmidt et al. (2013) found a significant reduction in risk of breast cancer recurrence when the highest level of physical activity from age 50y to breast cancer diagnosis (i.e. recent physical activity) was compared to the lowest.

Dose-response relationships for lifetime and recent pre-diagnosis physical activity

A statistically significant dose-response relationship between increasing levels of physical activity and decreased risk of all-cause death, breast cancer-related death and/or breast cancer recurrence was reported in four studies including an assessment of pre-diagnosis physical activity and in seven studies including post-diagnosis physical activity assessments.

Regarding lifetime physical activity, West-Wright et al. (2009) found a significant dose-response relationship between increasing physical activity and both all-cause and breast cancer-related death. Similarly, Friedenreich and colleagues (2009) observed a significant dose-response relationship between increasing lifetime household physical activity and all-cause death, increasing lifetime recreational physical activity and breast cancer-related death, increasing moderate-intensity recreational physical activity and both all-cause and breast cancer-related death and breast cancer recurrence and progression and new primaries.

When recent pre-diagnosis physical activity was considered, one study (Irwin et al., 2011) reported significant dose-response relationship between increasing moderate-vigorous recreational physical activity and all-cause death and moderate-intensity and all-cause death and breast cancer-related death. Similarly, another study (Irwin et al., 2008) found a dose-response relationship between recent pre-diagnosis recreational physical activity and all-cause death.

Post-diagnosis physical activity and all-cause death

Nine studies investigated the association between post-diagnosis physical activity and reduced risk of death in breast cancer survivors (Cadmus-Bertram et al., 2011; Chen et al., 2011; George et al., 2011; Irwin et al., 2011; Sternfield et al., 2009; Holick et al., 2008; Irwin et al., 2008; Pierce et al., 2007; Holmes et al., 2005). Six of the seven studies found statistically significant reduced risk of all-cause death when comparing breast cancer survivors who performed the highest versus the lowest levels of post-diagnosis recreational physical activity (Cadmus-Bertram et

al., 2011; Chen et al., 2011; Irwin et al., 2011; Holick et al., 2008; Irwin et al., 2008; Holmes et al., 2005), while one study found a non-significant reduced risk (Sternfield et al., 2009). Chen and colleagues (2011) assessed physical activity at six, 18 and 36 months post-diagnosis, and found significant risk reductions in all-cause death six months post-diagnosis with exercise participation (yes vs. no), and 18 months and 36 months post-diagnosis when the highest categories was compared to the lowest for exercise participation (yes vs. no, and $h \cdot wk^{-1}$) and exercise energy expenditure, but borderline significant reductions were observed six months post-diagnosis for highest category of hours per week of exercise and exercise energy expenditure versus the lowest.

In regards to the intensity of physical activity, two studies (Irwin et al., 2011; Holick et al., 2008) found a significant and one study (Sternfield et al., 2009) found a borderline significant risk reduction in all-cause death when comparing the highest amount of moderate-intensity recreational physical activity versus the lowest. Sternfield et al. (2009) and Holick et al. (2008) reported a non-significant reduction in risk and null-finding, respectively, when comparing the highest amount of vigorous-intensity recreational physical activity versus the lowest. Two studies in addition to a total physical activity variable, reported a combined moderate and vigorous-intensity physical activity variable (Cadmus-Bertram et al., 2012; Sternfield et al., 2009). These studies found a significant risk reduction (Cadmus-Bertram et al., 2012) and a non-significant reduction in risk (Sternfield et al., 2009) of all-cause death when comparing the highest versus lowest moderate-vigorous recreational physical activity categories.

An additional variable was created to investigate whether achieving recommended physical activity guidelines (150 min/week or ≥9-10 MET-h·wk^{-1}) conferred a reduction in the risk of all-cause death in breast cancer survivors. It was possible to include six studies of the post-diagnosis physical activity for this analysis (Cadmus-Bertram et al., 2011; Chen et al., 2011; Irwin et al., 2011; Irwin et al., 2008; Holmes et al., 2005). Five of the six studies observed a significant reduction in the risk of all-cause death when comparing those who achieved the recommended guidelines or more versus those who did less than the recommended amount (Cadmus-Bertram et al., 2011; Holmes et al., 2005) or those who did no physical activity (Chen et al., 2011; Irwin et al., 2011; Irwin et al., 2008), while another study found a non-significant reduction in risk in those who achieved the guidelines versus those who did not (Sternfield et al., 2009).

Post-diagnosis physical activity and breast cancer-related death

When the risk of breast cancer-related death in breast cancer survivors performing the highest level of recreational post-diagnosis physical activity was compared to that of survivors performing the lowest, significant reductions in risk was found in three studies (Irwin 2011; Holick et al., 2008; Holmes et al., 2005), while non-significant decreases in risk was found in two studies (Sternfield et al., 2009; Irwin et al., 2008). When the intensity of physical activity was considered, Holick and colleagues (2008) found a significant breast cancer-related risk reduction with the highest levels of moderate-intensity physical activity compared to the lowest, but reported a null-finding with vigorous-intensity physical activity. Irwin et al. (2011) observed a non-significant decrease in risk when comparing the highest category of vigorous-intensity compared to the lowest. Sternfield

and colleagues (2009) found when the highest categories were compared to the lowest, non-significant decreases in risk of breast cancer-related with moderate-vigorous intensity physical activity (MET-h·wk^{-1}) and hours per week of moderate-intensity physical activity, and null-findings for hours per week of vigorous-intensity physical activity. Of the three studies that investigated the association between meeting recommended guidelines and breast cancer-related death, one study each found a significant reduction (Irwin et al., 2011), a non-significant reduction (Irwin et al., 2008) and a null-finding (Sternfield et al., 2009).

Post-diagnosis physical activity and recurrence

Chen and colleagues (2011) combined breast cancer-related deaths with breast cancer recurrences and found significant risk reductions in these breast cancer events 18 and 36 months post-diagnosis when the highest categories was compared to the lowest for exercise participation (yes/no and h·wk^{-1}) and exercise energy expenditure. Non-significant reductions were observed six months post-diagnosis for exercise participation yes versus no and exercise energy expenditure highest versus the lowest category, while a null-finding was found for the highest compared to the lowest number of hours per week of exercise.

One study (Holmes et al., 2005) found a borderline significant while another study (Sternfield et al., 2009) reported a null-significant reduction in breast cancer recurrences with the highest versus the lowest category of total post-diagnosis recreational physical activity. Sternfield and colleagues (2009) also observed when the highest categories were compared to the lowest, non-significant decreases in risk of recurrence

with hours per week of moderate-intensity physical activity, and null-findings for moderate-vigorous intensity physical activity (MET-h·wk^{-1}), hours per week of vigorous-intensity physical activity and performance of at least nine MET-h·wk^{-1} of selected recreational activity. Cadmus-Bertram et al. (2011) combined breast cancer recurrences with new breast primaries and found non-significant decreases in risk with total recreational physical activity and moderate-vigorous intensity physical activity when the highest and lowest categories were compared, and also when those who achieved at least 10 MET-h·wk^{-1} of recreational physical activity were compared to those who performed less.

Dose-response relationships for post-diagnosis physical activity

Significant dose-response relationships between total post-diagnosis recreational physical activity and all-cause death and breast cancer-related death was found in seven (Cadmus-Bertram et al., 2011; Chen et al., 2011; Irwin et al., 2011; Sternfield et al., 2009; Holick et al., 2008; Irwin et al., 2008; Holmes et al., 2005) and three studies (Irwin et al., 2011; Holick et al., 2008; Holmes et al., 2005), respectively. Moderate-vigorous intensity physical activity was associated with a significant dose-response relationship with both all-cause death and breast cancer recurrences and new primaries in one study (Chen et al., 2011), while a significant does-response relationship between moderate-intensity physical activity and all-cause death in two studies (Irwin et al., 2011; Holick et al., 2008) and breast cancer-related death in another study (Holick et al., 2008). Holmes and colleagues (2005) observed a dose-response relationship between post-diagnosis recreational physical activity and breast cancer recurrence. Chen and colleagues (2011) observed a significant dose-response

between exercise participation at 36 months post-diagnosis and breast cancer-related deaths and breast cancer recurrences combined.

Change in physical activity from pre- to post-diagnosis

One study (Irwin et al., 2011) assessed the risk of all-cause and breast cancer-related death with a change in moderate-vigorous intensity physical activity pre-diagnosis to post-diagnosis. A significant reduction in all-cause death risk was found when comparing those who increased moderate-vigorous intensity physical activity versus those who had no change, while a null-finding was observed between breast cancer-related death and change in moderate-vigorous intensity physical activity.

Change in post-diagnosis physical activity

Cadmus-Bertram and colleagues (2011) observed null-findings when comparing the risk of all-cause death and breast cancer events (recurrences and new primaries combined) in those who went from non-adherence at baseline (post-diagnosis) to adherence to physical activity guidelines one-year post baseline versus those who did not adhere to guidelines at either assessment point. However, those who adhered to the guidelines at both assessment points had a significantly reduced risk of all-cause death compared to non-adherers at both points. The authors (2011) also reported non-significant reductions in all-cause death risk and a null-finding for breast cancer events when comparing the highest versus the lowest change in total physical activity. Similarly, no significant reductions were found in risk of all-cause death and breast cancer events when comparing the highest versus the lowest change in moderate-vigorous intensity physical activity.

Table 2.7.3 Physical activity and all-cause and breast cancer death and recurrence risk; results from epidemiological studies[†]

Trial	PA categories	Comparisons	All-cause deaths HR (95% CI)	Breast cancer deaths HR (95% CI)	Recurrences HR (95% CI)
Schmidt et al. (2013) (MARIE)	Pre-diagnosis recreational PA (Met-h·wk^{-1}) • 0 • >0 to <12 • 12 to <24 • 24 to <42 • ≥42	a) High vs. low PA category	a) HR=0.66 (0.47-0.92)	a) HR=0.80 (0.53-1.21)	a) HR=0.65 (0.44-0.97)
Cleveland et al. (2012) (LIBCSP)	a) Total pre-diagnosis lifetime recreational PA (Met-h·wk^{-1}) categories: • 0 • >0-8.9 • ≥9	a) Highest vs. lowest category	a) HR=0.57 (0.39-0.83)	a) 0.66 (0.42-1.06)	NR
	b) Pre-diagnosis moderate-intensity lifetime PA (Met-h·wk^{-1}) categories: • 0 • >0-8.9 • ≥9	b) Highest vs. lowest category	b) HR=0.66 (0.44-0.99)	b) HR=0.73 (0.44-1.2)	
	c) Pre-diagnosis vigorous-intensity lifetime recreational PA (Met-h·wk^{-1}) categories: • 0 • >0-8.9 • ≥9	c) Highest vs. lowest category	c) HR=0.68 (0.31-1.50)	c) HR=0.83 (0.35-1.97)	
Cadmus-Bertram et al. (2011) (WHEL)	a) Total PA (Met-h·wk^{-1}): • Q1: 0-2.5 • Q2: 2.5-7.5 • Q3: 7.5-14.9 • Q4: 14.9-24.7 • Q5: 24.7-107	a) Highest vs. lowest total PA quintile	a) HR=0.47 (0.26-0.84)**		a) HR=0.74 (0.50-1.10)
	b) Moderate-vigorous PA (Met-h·wk^{-1}): • Q1: 0-1.3 • Q2: 1.3-6.3	b) Highest vs. lowest moderate-to-vigorous PA quintile	b) HR=0.39 (0.21-0.72)**		b) HR=0.67 (0.45-1.00)*

Trial	PA categories	Comparisons	All-cause deaths HR (95% CI)	Breast cancer deaths HR (95% CI)	Recurrences HR (95% CI)
	• Q3: 6.3-12.5 • Q4: 12.5-22.9 Q5: 22.9-107				
	c) Meeting PA guideline: • Yes (≥ 10 Met-h·wk^{-1}) • No (<10 Met-h·wk^{-1})	c) Meeting PA guideline vs. not meeting PA guideline	c) HR=0.65 (0.47-0.91)**		c) HR=0.89 (0.70-1.14)
	d) Change in adherence to guideline: • No → No • No → Yes • Yes → No • Yes → Yes	d) i. No → Yes vs. No → No ii. Yes → Yes vs. No → No	d) i. HR=1.21 (0.77-1.90) ii. HR=0.60 (0.40-0.88)**		d) i. HR=1.44 (1.02-2.03)* ii. HR=0.93 (0.70-1.24)
	e) Change in total PA (Met-h·wk^{-1}) • Q1: -68.8, -5.5 • Q2: -5.5, -0.3 • Q3: -0.3, 2.3 • Q4: 2.3, 7.5 • Q5: 7.5, 92.3	e) Highest vs. lowest change in total PA quintile	e) HR=0.89 (0.49-1.64)		e) HR=1.19 (0.80-1.77)
	f) Change in moderate-to-vigorous PA (Met-h·wk^{-1}) • Q1: -68.8, -5.5 • Q2: -5.5, -0.3 • Q3: -0.3, 2.3 • Q4: 2.3, 7.5 • Q5: 7.5, 92.3	f) Highest vs. lowest change in moderate-to-vigorous PA quintile	f) HR=0.92 (0.51-1.66)		f) HR=1.23 (0.83-1.80)
Chen et al. (2011) (SBCSS)	a) Exercise participation • Yes • No	a) Yes vs. no exercise participation for i. First 6 mo post-diagnosis ii. First 18 mo post-diagnosis iii. First 36 mo post-diagnosis	a) i. HR=0.80 (0.65-0.97) ii. HR=0.70 (0.56-0.87) iii. HR=0.70 (0.56-0.88)	a) i. HR=0.91 (0.75-1.11) ii. HR=0.71 (0.57-0.90) iii. HR=0.60 (0.47-0.76)	

Trial	PA categories	Comparisons	All-cause deaths HR (95% CI)	Breast cancer deaths HR (95% CI)	Recurrences HR (95% CI)
	b) Exercise participation (h·wk^{-1}) • No exercise • <2.5 • ≥2.5	b) ≥2.5 h·wk^{-1} exercise vs. no exercise i. First 6 mo post-diagnosis ii. First 18 mo post-diagnosis iii. First 36 mo post-diagnosis	b) i. HR=0.82 (0.64-1.04) ii. HR=0.66 (0.51-0.84)** iii. HR=0.64 (0.49-0.82)**	b) i. HR=1.01 (0.80-1.27) ii. HR=0.73 (0.57-0.94) iii. HR=0.57 (0.44-0.74)*	
	c) Exercise energy expenditure (Met-h·wk^{-1}) • No exercise • <8.3 • ≥8.3	c) ≥8.3 Met-h·wk^{-1} vs. no exercise i. First 6 mo post-diagnosis ii. First 18 mo post-diagnosis iii. First 36 mo post-diagnosis	c) i. HR=0.80 (0.63-1.02) ii. HR=0.65 (0.51-0.83)** iii. HR=0.65 (0.51-0.84)**	c) i. HR=0.98 (0.78-1.24) ii. HR=0.72 (0.57-0.93) iii. HR=0.59 (0.45-0.76)	
George et al. (2011) (HEAL)	a) Recreational PA (Met-h·wk^{-1}) categories: • 0 • >0 Diet quality quartiles: • Q1. Poor quality • Q2-3. Mixed quality • Q4. Better quality	a) 0 Met-h·wk^{-1} and poor quality diet vs. >0 Met-h·wk^{-1} and poor quality diet category b) 0 Met-h·wk^{-1}and poor quality vs.>0 Met-h·wk^{-1} and better quality category	a) HR=0.53 (0.21-1.34) b) HR=0.11 (0.04-1.36)	a) HR=1.05 (0.25-4.45) b) HR=0.09 (0.01-0.89)	NR
Irwin et al. (2011) (WHI)	a) Pre-diagnosis moderate-vigorous intensity PA (Met-h·wk^{-1}) categories: • 0 • <3 • 3.1-8.9 • ≥9	a) Highest vs. lowest category	a) HR=0.61 (0.47-0.81)**	a) HR=0.71 (0.49-1.03)	NR

Trial	PA categories	Comparisons	All-cause deaths HR (95% CI)	Breast cancer deaths HR (95% CI)	Recurrences HR (95% CI)
	b) Pre-diagnosis moderate-intensity PA (Met-h·wk^{-1}) categories: • 0 • <3 • 3.1-8.9 • ≥9	b) Highest vs. lowest category	b) HR=0.58 (0.44-0.78)**	b) HR=0.60 (0.4-0.9)*	
	c) Post-diagnosis moderate-vigorous intensity PA (Met-h·wk^{-1}) categories: • 0 • <3 • 3.1-8.9 • ≥9	c) Highest vs. lowest category	c) HR=0.54 (0.38-0.79)**	c) HR=0.61 (0.35-0.99)*	
	d) Post-diagnosis moderate-intensity PA (Met-h·wk^{-1}) categories: • 0 • <3 • 3.1-8.9 • ≥9	d) Highest vs. lowest category	d) HR=0.62 (0.41-0.93)*	d) HR=0.66 (0.36-1.21)	
	e) Change in moderate- to vigorous-intensity PA from pre-diagnosis to post-diagnosis • No change (stayed in either >0 to <9 Met-h·wk^{-1} or ≥9 Met-h·wk^{-1}) • Decrease (went from ≥9 Met-h·wk^{-1} pre-diagnosis to >0 to <9 Met-h·wk^{-1} post-diagnosis) • Increase (went from >0 to <9 Met-h·wk^{-1} pre-diagnosis to ≥9 Met-h·wk^{-1} post-diagnosis)	e) Increase vs. no change in PA category	e) HR=0.67 (0.46-0.96)	e) HR=0.91 (0.51-1.64)	
Emaus et al. (2010)	Pre-diagnosis recreational PA • Sedentary • Moderate • Regular exercise	a) Regular exercise vs. sedentary	a) HR=0.74 (0.51-1.08)	a) HR=0.75 (0.49-1.15)	NR

Trial	PA categories	Comparisons	All-cause deaths HR (95% CI)	Breast cancer deaths HR (95% CI)	Recurrences HR (95% CI)
Hellmann et al. (2010) (CHCS)	a) Pre-diagnosis recent recreational PA categories: • Inactive • Moderate PA of 2-4 h·wk^{-1} • High PA of >4 h·wk^{-1}	a) High PA > 4 h·wk^{-1} vs. inactive	a) HR=1.00 (0.69-1.45)	a) HR=1.01 (0.62-1.63)	NR
Keegan et al. (2010) (BCFR)	a) Lifetime recreational PA (Met-h·wk^{-1}) quartiles: • Q1: ≤6.7 • Q2: 6.8-16.3 • Q3: 16.4-26.1 • Q4: 26.2-46.0	a) Highest vs. lowest lifetime PA quartile	a) HR=0.93 (0.72-1.21)	NR	NR
	b) Pre-diagnosis recent PA (Met-h·wk^{-1}) (3y pre-diagnosis) • 0 • Q1: ≤9.9 • Q2: 10-17.7 • Q3: 17.8-38.2 • Q4: >38.2	b) Highest vs. lowest recent PA quartile vs. 0 PA	b) HR=0.77 (0.60-1.00)		
Friedenreich et al. (2009)	a) Total pre-diagnosis lifetime PA (Met-h·wk^{-1}·y^{-1}) • Q1: ≥95 • Q2: >95-≤120 • Q3: >120-≤151 • Q4:>151	a) Highest vs. lowest quartile	a) HR=0.94 (0.69-1.30)	a) HR=0.79 (0.53-1.17)	a) HR=1.22 (0.89-1.68)
	b) Pre-diagnosis occupational PA (MET-h·wk^{-1}·y^{-1}) • Q1: ≥27 • Q2: >27-≤43 • Q3: >43-≤62 • Q4:>62	b) Highest vs. lowest quartile	b) HR=0.97 (0.69-1.36)	b) HR=0.90 (0.58-1.39)	b) HR=1.07 (0.75-1.51)

Trial	PA categories	Comparisons	All-cause deaths HR (95% CI)	Breast cancer deaths HR (95% CI)	Recurrences HR (95% CI)
	c) Pre-diagnosis household PA (MET-h·wk^{-1}·y^{-1}) • Q1: ≥36 • Q2: >36-≤58 • Q3: >58-≤87 • Q4: >87	c) Highest vs. lowest quartile	c) HR=1.46 (1.02-2.09)*†	c) HR=1.25 (0.81-1.94)	c) HR=1.27 (0.9-1.8)
	d) Pre-diagnosis recreational PA (MET-h·wk^{-1}·y^{-1}) • Q1: ≥5 • Q2: >5-≤10 • Q3: >10-≤19 • Q4:>19	d) Highest vs. lowest quartile	d) HR=0.73 (0.53-1.00)	d) HR=0.54 (0.36-0.79)**	d) HR=0.76 (0.55-1.03)
	e) Moderate-intensity (3-6 METs) recreational PA (h·wk^{-1}·y^{-1}) categories: • 0-<1.4 • 1.4-<3.9 • ≥3.9	e) Highest vs. lowest category	e) HR=0.76 (0.58-1.06)**	e)HR=0.56 (0.38-0.82)*	e) HR=0.66 (0.48-0.91)**
	f) Vigorous-intensity (>6 METs) recreational PA (h·wk^{-1}·y^{-1}) categories: • <0.03 • ≥0.03	f) Highest vs. lowest category	f) HR=0.86 (0.68-1.07)	f) HR=0.74 (0.56-0.98)	f) HR =0.95 (0.76-1.19)
Sternfield et al. (2009) (LACE)	a) Total PA (Met-h·wk^{-1}) quartiles: • Q1: <29 • Q2: 29-<44 • Q3: 44-<62 • Q4: ≥62	a) Highest vs. lowest total PA quartile	a) HR=0.76 (0.48-1.19)	a) HR=0.87 (0.48-1.59)	a) HR=0.91 (0.61-1.36)
	b) Moderate-vigorous PA (Met-h·wk^{-1}) quartiles: • Q1: <5.3 • Q2: 5.3-<15 • Q3: 15-<27 • Q4: ≥27	b) Highest vs. lowest moderate-vigorous l PA quartile	b) HR=0.74 (0.49-1.13)	b) HR=0.90 (0.51-1.58)	b) HR=1.00 (0.68-1.46)

Trial	PA categories	Comparisons	All-cause deaths HR (95% CI)	Breast cancer deaths HR (95% CI)	Recurrences HR (95% CI)
	c) h·wk^{-1}of moderate PA: • <1 h·wk^{-1} • 1–<3 h·wk^{-1} • 3–<6 h·wk^{-1} • ≥6 h·wk^{-1}	c) Highest vs. lowest moderate PA category	c) HR=0.66 (0.42-1.03)*	c) HR=0.73 (0.40-1.33)	c) HR=0.81 (0.54-1.22)
	d) h·wk^{-1} of vigorous PA: • none • >0–<1 • ≥1	d) Highest vs. lowest vigorous PA category	d) HR=1.02 (0.70-1.47)	d) HR=1.10 (0.68-1.80)	d) HR=1.12 (0.81-1.56)
	e) NHS activity score (Met-h·wk^{-1}): • <9 • ≥9	e) Highest vs. lowest NHS activity score category	e) HR=0.98 (0.71-1.35)	e) HR=1.19 (0.78-1.84)	e) HR=1.16 (0.87-1.55)
West-Wright et al. (2009) (CTS)	a) Lifetime PA (h·wk^{-1}·y^{-1}): • Low PA (>0.5) • Intermediate PA (>0.5 and ≤3 but not >3) • High PA (≥1 of moderate or strenuous activity >3)	a) High vs. low PA category	a) HR=0.73 (0.55-0.96)*	a) HR=0.53 (0.35-0.80)**	NR
	b) Pre-diagnosis recent PA (h·wk^{-1}·y^{-1}) • Low PA (>0.5) • Intermediate PA (>0.5 and ≤3 but not >3) • High PA (≥1 of moderate or strenuous activity >3)	b) High vs. low PA category	a) HR=0.78 (0.60-1.02)	b) HR=1.08 (0.73-1.58)	
Dal Maso et al. (2008) (PACE)	a) Pre-diagnosis occupational PA at age 30-39y • Sitting, standing • Medium • Heavy, strenuous	a) Heavy, strenuous vs. sitting, standing	a) HR=1.18 (0.90-1.56)	a) HR=1.11 (0.81-1.52)	
	b) Pre-diagnosis recreational PA (h·wk^{-1}) • <2 • ≥2	b) ≥2 vs. <2 h·wk^{-1} of leisure time PA	b) HR=0.82 (0.67-1.01)	b) HR=0.85 (0.68-1.07)	

Trial	PA categories	Comparisons	All-cause deaths HR (95% CI)	Breast cancer deaths HR (95% CI)	Recurrences HR (95% CI)
Holick et al. (2008) (CWLS)	a) Post-diagnosis total recreational PA (Met-h·wk^{-1}) quartiles: • Q1: <2.7 • Q2: 2.7-7.9 • Q3: 8.0-20.9 • Q4: ≥21.0	a) Highest vs. lowest total recreational PA quartile	a) HR=0.44 (0.32-0.60)**	a) HR=0.51 (0.29-0.89)*	NR
	b) Post-diagnosis moderate-intensity recreational PA (Met-h·wk^{-1}) quartiles: • Q1: <2.0 • Q2: 2.0-3.9 • Q3: 4.0-10.2 • Q4: ≥10.3	b) Highest vs. lowest total moderate-intensity PA quartile	b) HR=0.46 (0.34-0.63)**	b) HR=0.47 (0.26-0.83)*	
	c) Post-diagnosis vigorous-intensity PA (Met-h·wk^{-1}) quartiles: • Q1: 0.0 • Q2: 0.1-5.9 • Q3: 6.0-15.0 • Q4: ≥15.1	c) Highest vs. lowest total vigorous-intensity PA quartile	c) HR=0.82 (0.58-1.16)	c) HR=1.02 (0.53-1.97)	
Irwin et al. (2008) (HEAL)	a) Pre-diagnosis recreational PA (Met-h·wk^{-1}) tertiles: • 0 • >0-<9 • ≥9	a) Highest vs. lowest PA tertile	a) HR=0.69 (0.45-1.06)*	a) HR=0.83 (0.45-1.38)	NR
	b) Post-diagnosis recreational PA (Met-h·wk^{-1}) tertiles: • 0 • >0-<9 • ≥9	b) Highest vs. lowest PA tertile	b) HR=0.33 (0.15-0.73)*	b) HR=0.65 (0.23-1.87)	
Pierce et al. (2007) (WHEL)	a) Total PA (Met-h·wk^{-1}) quartiles: • Q1: 0-3.75 • Q2: 3.75-10.6 • Q3: 10.6-22 • Q4: 22-107	a) Highest vs. lowest total PA quartile	a) HR= 0.58* (NR)	NR	NR

Trial	PA categories	Comparisons	All-cause deaths HR (95% CI)	Breast cancer deaths HR (95% CI)	Recurrences HR (95% CI)
	b) Diet and PA categories: • Low vegetables and fruit (VF) and low PA • Low VF and high PA • High VF and low PA • High VF and high PA	b) Low VF and low PA vs. high VF and low PA c) Low VF and low PA vs. high VF and high PA	b) HR= 0.86 (0.51-1.45) c) HR=0.56 (0.31-0.98)*		
Abrahamson et al. (2006)	Average recreational PA 1 year pre-diagnosis quartiles (relative units): • Q1: 1.6-3.4 • Q2: 3.5-13.5 • Q3: 13.6-35.0 • Q4: 35.1-98.0	a) Highest vs. lowest quartile for year pre-diagnosis	a) HR=0.78 (0.56-1.08)	NR	NR
	b) Average recreational PA age 13y, age 20y and year before diagnosis quartiles (relative units): • Q1: 1.6-16.6 • Q2:16.7-29.4 • Q3: 29.5-43.0 • Q4: 43.1-98.0	b) Highest vs. lowest quartile for average of 3 periods pre-diagnosis	b) HR=1.16 (0.84-1.60)		
Holmes et al. (2005) (NHS)	a) Post-diagnosis recreational PA (Met-h·wk^{-1}) categories: • < 3 • 3 to 8.9 • 9 to 14.9, • 15 to 23.9 • ≥24	a) Highest vs. lowest PA category	a) HR=0.65 (0.48-0.88)**	a) HR=0.60 (0.40-0.89)**	a) HR=0.74 (0.53-1.04)*
Borugian et al. (2004)	Pre-diagnosis: a) Flights of stairs climbed: • none • 1-4 • 5-8 • 9+	a) Highest vs. lowest category climbing stairs	NR	a) HR=1.1 (0.5-2.2)	NR

Trial	PA categories	Comparisons	All-cause deaths HR (95% CI)	Breast cancer deaths HR (95% CI)	Recurrences HR (95% CI)
	b) Number of blocks walked: • none • 1-4, • 5-8 • 9+	b) Highest vs. lowest category walking		b) HR=1.0 (0.5-1.9)	
	c) Sports: • none • a few times a year • a few times a month • about once a week • more than once a week	c) Highest vs. lowest category sports		c) HR=1.0 (0.5-3.2)	
	d) Exercise: • none • few times/year, few times /month • about once a week • more than once a week	d) Highest vs. lowest category exercise		d) HR=1.0 (0.6-1.6)	
	e) Jogging: • none • a few times a year • a few times a month • about once a week • more than once a week	e) Highest vs. lowest category jogging		e) HR=1.8 (0.4-7.5)	
	f) Swimming: • none • few times/year, few times /month • about once a week • more than once a week	f) Highest vs. lowest category swimming		f) HR=0.9 (0.5-1.5)	
	g) Gardening • none • a few times a year • a few times a month • about once a week • more than once a week	g) Highest vs. lowest category gardening		g) HR=0.8 (0.5-1.4)	

Trial	PA categories	Comparisons	All-cause deaths HR (95% CI)	Breast cancer deaths HR (95% CI)	Recurrences HR (95% CI)
Enger and Bernstein, (2004)	a) Average hours of PA per week from first menses to 1-y prior to diagnosis	a) 3.8 average h·wk^{-1} of PA vs. 0 average h·wk^{-1} PA		a) HR=1.30 (0.81-2.09)	
	b) Average hours of PA per week during year before 1-y prior to diagnosis	b) 5+ average h·wk^{-1} vs. 0 average h·wk^{-1} of PA		b) HR=0.78 (0.45-1.34)	
	c) h·wk^{-1}from first menses to 1-y prior to diagnosis and year before 1-y pre-diagnosis	c) 3.8 h·wk^{-1} from first menses to 1-y prior to diagnosis and 1+h·wk^{-1} in the year before 1-y pre-diagnosis vs. 0 and 0 h·wk^{-1}		c) HR=1.26 (0.68-2.32)	
Rohan et al. (1995)	a) Total pre-diagnosis recreational PA categories (kcal·min^{-1}) • 0 • >0-≤2,000 • >2,000-≤4,000 • >4,000	a) >4,000 vs. 0 kcal·min^{-1} of recreational activity		a) HR=0.98 (0.5-1.94)	
	b) Total light recreational PA categories (kcal·min^{-1}) • 0 • >0-≤2,000 • >2,000	b) >2,000 total light recreational PA vs. 0 recreational PA		b) HR=1.07 (0.61-1.89)	
	c) Total moderate recreational PA categories (kcal·min^{-1}) • 0 • >0	c) >0 moderate recreational PA vs. 0 recreational PA		c) HR=0.51 (0.24-1.06)	
	d) Total vigorous recreational PA categories (kcal·min^{-1}) • 0 • >0	d) >0 vigorous recreational PA vs. 0 recreational PA		d) HR=1.75 (0.68-4.47)	

† Only results from multivariate adjusted comparisons are reported. Full multivariate analysis details can be found in appendix C.
* P-value ≤ 0.05 ** P-value ≤ 0.01

Sub-analyses by menopausal status or age

Only one of the studies (Emaus et al., 2010) that assessed pre-diagnosis physical activity included sub-analyses of overall and/or breast cancer mortality stratified by age or menopausal status. Emaus and colleagues (2010) reported a significant reduction in the risk of all-cause death in the highest physical activity group versus the lowest in postmenopausal but not for premenopausal participants. Four studies that assessed post-diagnosis physical activity included this sub-analyses (Chen et al., 2011; Holick et al., 2008; Irwin et al., 2008; Holmes et al., 2005) (see appendix D for full details of subanalyses). However, the definition of menopausal status differed across studies. Two of these studies separated breast cancer survivors into used self-reported menopausal status (Chen et al., 2011; Holmes et al., 2005), while the other two studies (Holick et al., 2008; Irwin et al., 2008) separated women depending on the study populations average age (above or below 59 and above or below 55, respectively). One study (Irwin et al., 2008) observed significant reductions in all-cause death in participants aged 55y or under who performed any amount of physical activity versus women who performed no physical activity. One study reported a significant reduction in breast cancer-related death in participants aged 59y or under when comparing those who engaged in eight MET-h·wk^{-1} or above versus those who performed less (Holick et al., 2008), while another reported borderline significant reductions in pre-menopausal women when comparing those who achieved 9 MET-h·wk^{-1} or above versus those who performed less (Holmes et al., 2005).

Significant reductions in all-cause death were found in two studies (Chen et al., 2011; Irwin et al., 2008) and significant reductions in breast cancer-

related death was found in one study (Holmes et al., 2005) for postmenopausal or those breast cancer survivors aged above the average study population when comparing engagement in higher levels of physical activity versus lower or no physical activity. Chen et al. (2011) found significant and borderline significant reductions in breast cancer events (breast cancer-related deaths + recurrences) in post-menopausal and premenopausal participants, respectively, in the highest physical activity group compared to the lower physical activity group.

Sub-analyses by BMI

Three studies that assessed lifetime pre-diagnosis physical activity included subanalyses of overall and/or breast cancer mortality stratified by BMI (Cleveland et al., 2012; West-Wright et al., 2009; Abrahamson et al., 2006) (see appendix D). These studies reported mixed results. Two studies (Cleveland et al., 2012; West-Wright et al., 2009) found significant risk reductions in all-cause death for women with a BMI <25 $m \cdot kg^2$ performing the highest amount of physical activity versus those performing the lowest. Cleveland and colleagues (2012) reported a borderline significant reduction for those with a BMI ≥25 $m \cdot kg^2$, but non-significant reductions in breast cancer-related death for women with a BMI above and below 25 $m \cdot kg^2$ for women. West-Wright et al. (2009) found significant risk reductions in breast cancer-related death for those with a BMI ≥25 $m \cdot kg^2$ for women categorised as high activity versus low activity, but null-findings for with BMI <25 $m \cdot kg^2$, and non-significant reductions in all-cause regardless of BMI category. Abrahamson et al. (2006) found significant risk reductions in all-cause death for women with a BMI ≥25 $m \cdot kg^2$ and achieving above the median physical activity level of the study population

versus those performing below the median physical activity, but null-findings for women with a BMI <25 $m \cdot kg^2$. Keegan et al. (2010) compared women who performed any physical activity in the three years pre-diagnosis versus those who performed no physical activity, and reported null-findings for effects on all-cause death regardless of BMI categories.

Seven studies that assessed post-diagnosis physical activity included subanalyses of overall and/or breast cancer mortality stratified by BMI (Schmidt et al., 2013; Chen et al., 2011; Irwin et al., 2011; Sternfield et al., 2009; Holick et al., 2008; Irwin et al., 2008; Holmes et al., 2005). Two of these studies (Irwin et al., 2011; Sternfield et al., 2009) stratified based on three BMI categories (<25, ≥25-29.9 and ≥30 $kg \cdot m^2$), and both found significant reductions in risk of all-cause death for breast cancer survivors with BMI below 25 when comparing breast cancer survivors with higher levels of physical activity versus those with lower levels. However, Irwin and colleagues (2011) found significant reductions for the ≥25 to 29.9 $kg \cdot m^2$ category also. No other significant risk reductions were found in any of the other BMI categories in the two studies.

The remaining five studies stratified BMI based on two categories (<25 and ≥25 $kg \cdot m^2$). Of these four studies, one study (Chen et al., 2011) observed significant reductions in all-cause death in women with BMI less than 25 $kg \cdot m^2$ when comparing survivors who performed 8.3 MET-$h \cdot wk^{-1}$ of physical activity or above versus those who performed none, while conversely another (Irwin et al., 2008) observed significant reductions with BMI of 25 $kg \cdot m^2$ or above in survivors who engaged in any physical activity versus those who engaged in none. Conflicting results were also observed

in those studies that analysed breast-cancer related death stratified by BMI (Holick et al., 2008; Holmes et al., 2005). Holick et al. (2008) found no difference in breast cancer-related death between BMI categories when comparing women performing 8 MET-h·wk^{-1} or above of physical activity versus those performing under this amount, while, Holmes et al. (2005) found significant reductions in only the <25 kg·m^{2} BMI category when comparing women with ≥24 MET-h·wk^{-1} of physical activity versus those performing less than three MET-h·wk^{-1}. Schmidt et al. (2013) reported null-findings for the risk of all-cause and breast cancer-related death in each of the BMI categories when comparing the most active participants versus the least. Finally, Chen et al. (2011) found significant reductions in breast cancer events (breast-cancer-related deaths + recurrences) for women in both BMI categories when women who performed 8.3 MET-h·wk^{-1} of physical activity or above were compared to those who performed none.

Sub-analyses by breast cancer stage

One study (West-Wright et al., 2009) that assessed pre-diagnosis physical activity and five studies that assessed post-diagnosis physical activity included sub-analyses of overall and/or breast cancer mortality stratified by breast cancer stage (Chen et al., 2011; Irwin et al., 2011; Holick et al., 2008; Irwin et al., 2008; Holmes et al., 2005). West-Wright and colleagues (2009) reported significant reductions in breast cancer-related death for both localised and non-localised breast cancer when comparing women who achieved over three hours of lifetime physical activity per week per year versus women who performed less than 30 min of lifetime physical activity per week per year, but only borderline significant reductions and non-significant reductions in all-cause death for localised and non-

localised breast cancer, respectively. The authors (2009) also compared women who achieved over three hours of physical activity per week per year in the three years pre-diagnosis versus women who performed less than 30 minutes of physical activity per week per year in the same period, and found no significant reductions in all-cause or breast cancer related-death for either for localised and non-localised breast cancer.

Of the five studies involving post-diagnosis physical activity that stratified by breast cancer stage, four (Chen et al., 2011; Irwin et al., 2011; Irwin et al., 2008; Holmes et al., 2005) used the TNM classification system while the other study SEER Programme summary staging (Holick et al., 2008). Only one study (Irwin et al., 2011) found a significant reduction in all-cause death and none of the studies found significant reductions in breast cancer-related death for early stage (stage I, stage I-IIa or localised) breast cancer when the higher physically active participants were compared to the lower or lowest physically active. Conversely, three of the studies found significant reductions in all-cause death (Chen et al., 2011; Irwin et al., 2011; Irwin et al., 2008) and two (Holick et al., 2008; Holmes et al., 2005) found significant reductions in breast cancer-related death in more advanced (Stage II-III or regional) when comparing the more physically active participants versus the lower or lowest. In addition, Holmes and colleagues (2005) found a higher reduction in breast cancer-related death in those physically active participants with stage III breast cancer than those physically active participants with stage II or I. Chen et al. (2011) found a significant reduction in breast cancer events (recurrence + breast cancer-related deaths) in women with both stage I-IIa and IIB-III with higher levels of physical activity versus lower or no physical activity.

Sub-analyses by ER status

Two studies that assessed pre-diagnosis physical activity included sub-analyses of overall and/or breast cancer mortality stratified by ER status (Keegan et al., 2010; West-Wright et al., 2009). Both studies assessed physical activity in the three years prior to diagnosis, while one study also included lifetime physical activity (West-Wright et al., 2009). In these two studies, only Keegan et al. (2010) found a significant reduction in all-cause death in women diagnosed with ER-positive breast cancer when comparing women who achieved over 38.2 MET-h·wk^{-1} of physical activity versus women who performed no physical activity. However, West-Wright and colleagues (2009) found significant reductions in breast cancer-related death in women diagnosed with ER-positive breast cancer and significant reductions in both all-cause and breast cancer-related death in women with ER-negative when comparing women who achieved over three hours of lifetime physical activity per week per year versus women who performed <30 min of lifetime physical activity per week per year.

Four studies assessing post-diagnosis physical activity included sub-analyses of overall and/or breast cancer mortality stratified by ER and/or PR status (Chen et al., 2011; Irwin et al., 2011; Sternfield et al., 2009; Irwin et al., 2008; Holmes et al., 2005). No significant reductions in all-cause death for ER-positive was found in the four studies when comparing higher amounts of physical activity to either low physical activity or no activity. Although, Holmes et al. (2005) found significant reductions in breast cancer-related death for ER-positive breast cancer. Conversely, three (Chen et al., 2011; Irwin et al., 2011; Irwin et al., 2008) of the four studies found significant reductions in all-cause death in women with ER-

negative and/or PR-negative breast cancer when comparing higher physical activity to either low physical activity or no activity. The other study (Sternfield et al., 2009) found a non-significant decrease in all-cause death. Holmes et al. (2005) found no significant reductions breast cancer-related death for ER-negative, whereas, Chen et al., (2011) found a significant reduction in breast cancer events (recurrence + breast cancer-related deaths) in women with ER-negative breast cancer with higher levels of physical activity versus lower or no physical activity.

Sub-analyses of other characteristics

In Irwin et al. (2008) other sub-analyses included by race (African American, Hispanic white and non-Hispanic white women) and adjuvant treatment received (surgery only, radiation and any chemotherapy). From the race analyses, reduced all-cause mortality risk with physical activity two years post-diagnosis was found only in non-Hispanic white women (HR=0.26; 0.10 to 0.65). While, there was no significant association between all-cause mortality and physical activity in any of the treatment sub-analyses (Irwin et al., 2008). Chen and colleagues (2011) analysed associations of exercise over the first 36 months after breast cancer diagnosis with total mortality and relapse/disease-specific mortality, stratified by HRQoL and co-morbidities. The authors reported that exercise of at least 8.3 MET-h·wk^{-1} compared to no exercise had a stronger effect on those women with a HRQoL score below the median than those women with scores equal to or above the median (HR=0.50; 0.35- to 0.71, p_{trend} <0.001 vs. 0.83; 0.58 to 1.21). The effect of exercise was also slightly stronger for women with a score on less than one on the Charlson co-morbidity index compared to women who scored at least one (HR=0.68;

0.50 to 0.90, p_{trend}=0.003 vs. HR=0.62 (0.37 to 1.05, p_{trend}=0.05). Schmidt et al. (2013) reported null-findings for the risk of all-cause and breast cancer-related death in those who smoked versus those who did not when comparing the most active participants to the least.

2.7.4.4 Meta-analysis of the results of studies

Lifetime pre-diagnosis recreational physical activity

Forest plots for each comparison are shown between figures 2.7.1 and 2.7.7. The summary HR (95% CI) was 0.81 (0.68 to 0.93) in a random effects model for all-cause death for breast cancer survivors with the highest levels of self-reported lifetime pre-diagnosis recreational physical activity compared to the lowest. Although, there was evidence of some heterogeneity among these studies, this did not reach statistical significance (Q=10.37, P>0.10, I^2=42.13%). The summary HR (95% CI) was 0.77 (0.57 to 1.04) in a random effects model for breast cancer-related death for breast cancer survivors with the highest levels self-reported lifetime pre-diagnosis recreational physical activity compared to the lowest. There was statistically significant heterogeneity among these studies (Q=16.54, P<0.10, I^2=69.77%), suggesting that systematic effect size variability was unaccounted for.

Recent pre-diagnosis recreational physical activity

The random effects model average effect size for all-cause death was 0.75 (0.68 to 0.84) when the highest levels of self-reported recent pre-diagnosis recreational physical activity was compared to the lowest. There was no evidence of statistically significant heterogeneity across studies (Q=4.93, P>0.1, I^2=-21.65%). For breast cancer-related death, the random

effects model summary HR was 0.87 (0.76 to 0.99) when comparing the highest levels of self-reported recent pre-diagnosis recreational physical activity to the lowest. There was evidence of substantial heterogeneity among these studies (Q=12.74, P<0.10, I^2=-69.74%).

Post-diagnosis recreational physical activity

The random effects model average effect size for all-cause death was 0.57 (0.48 to 0.67) when the highest level of self-reported post-diagnosis recreational physical activity was compared to the lowest. There was no evidence of statistically significant heterogeneity across studies (Q=8.25, P>0.1, I^2=-27.28%). For breast cancer-related death, the random effects model summary HR was 0.61 (0.55 to 0.68) when comparing the highest levels of self-reported post-diagnosis recreational physical activity to the lowest. Although the Q value was not statistically significant, the I^2 statistic revealed evidence of substantial heterogeneity among these studies (Q=1.72, P>0.10, I^2=-132.34%).

Post-diagnosis meeting recommended physical activity guidelines

The summary HR was 0.65 (0.53 to 0.79) in a random effects model for all-cause death for breast cancer survivors meeting recommended physical activity guidelines post-diagnosis compared to those who were not. There was statistically significant heterogeneity among these studies (Q=10.10, P<0.10, I^2=50.51%). An analysis of the effects of meeting recommended physical activity guidelines post-diagnosis on breast cancer-related death was not possible as there were not enough studies that included this as an outcome measure.

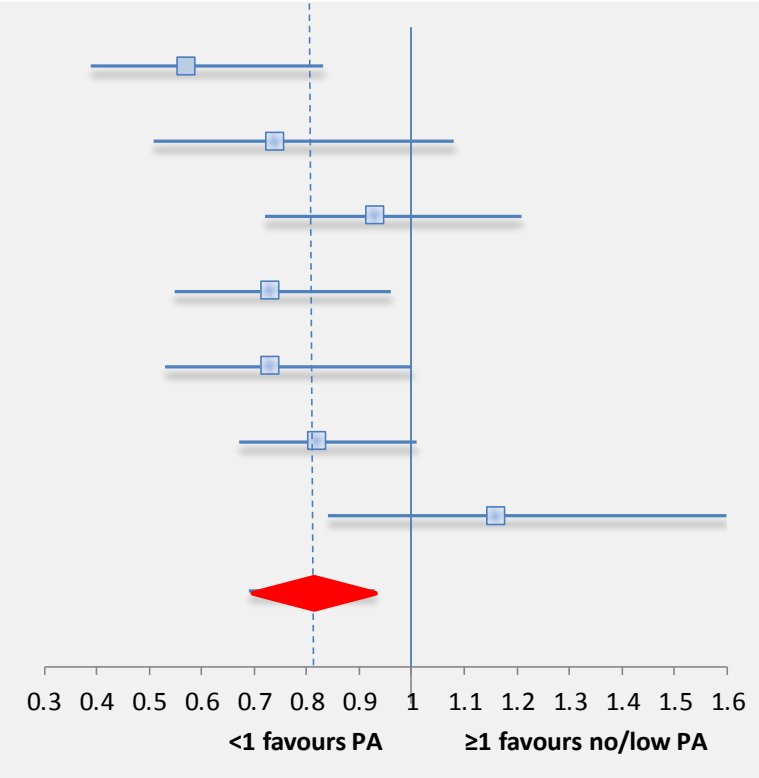
Study	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Cohort/Deaths	Weight (%) random effects analysis
Cleveland et al. 2012		0.57 (0.39 to 0.83)	1508/196	12.97
Emaus et al. 2010		0.74 (0.51 to 1.08)	1364/429	20.66
Keegan et al. 2010		0.93 (0.72 to 1.21)	3833/623	13.21
West-Wright et al. 2009		0.73 (0.55 to 0.96)	3539/460	15.41
Friedenreich et al. 2009		0.73 (0.53 to 1.00)	1225/341	16.63
Dal Maso et al. 2008		0.82 (0.67 to 1.01)	1453/503	10.61
Abrahamson et al. 2006		1.16 (0.84 to 1.6)	1264/290	10.51
Overall Random effects model (I^2=42.13 %)		**0.81 (0.68 to 0.93)**	**14186/2768**	**100.00**

Figure 2.7.1 Forest plot with random effects overall hazard ratio for association between **lifetime recreational (pre-diagnosis) physical activity** (highest vs. lowest physical activity categories) and **all-cause death** in breast cancer survivors

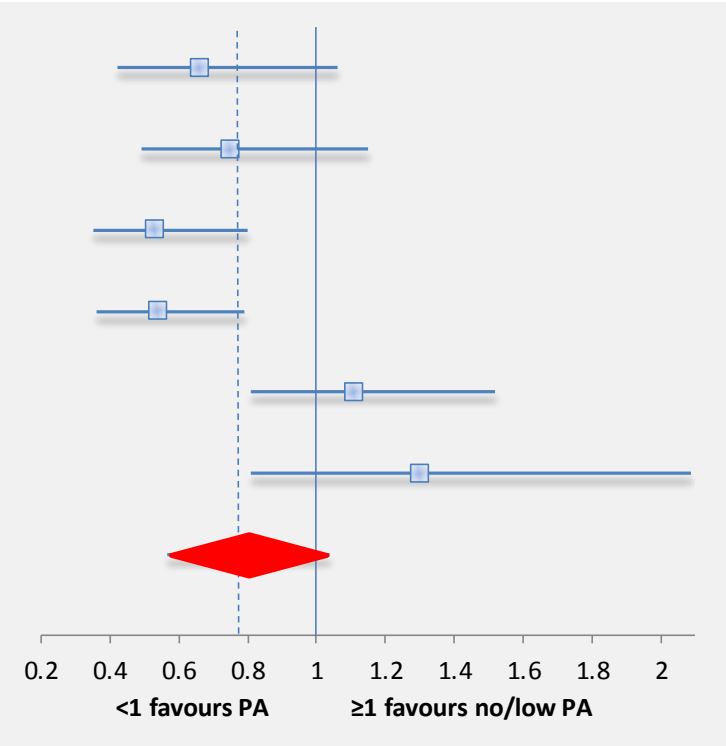
Study	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Cohort/Deaths	Weight (%) random effects analysis
Cleveland et al. 2012		0.66 (0.42 to 1.06)	1508/128	15.19
Emaus et al. 2010		0.75 (0.49 to 1.15)	1364/355	19.16
West-Wright et al. 2009		1.53 (0.35 to 0.80)	3539/221	17.18
Friedenreich et al. 2009		0.54 (0.36 to 0.79)	1225/223	16.67
Dal Maso et al. 2008		1.11 (0.81 to 1.52)	1453/398	16.34
Enger and Bernstein, 2004		1.30 (0.81 to 2.09)	717/251	15.45
Overall:		**0.77 (0.57 to 1.04)**	**9806/1576**	**100.00**
Random effects model				
(I^2= 69.77%)				

Figure 2.7.2 Forest plot with random effects overall hazard ratio for association between **lifetime recreational (pre-diagnosis) physical activity** (highest vs. lowest physical activity categories) and **breast cancer-related death** in breast cancer survivors

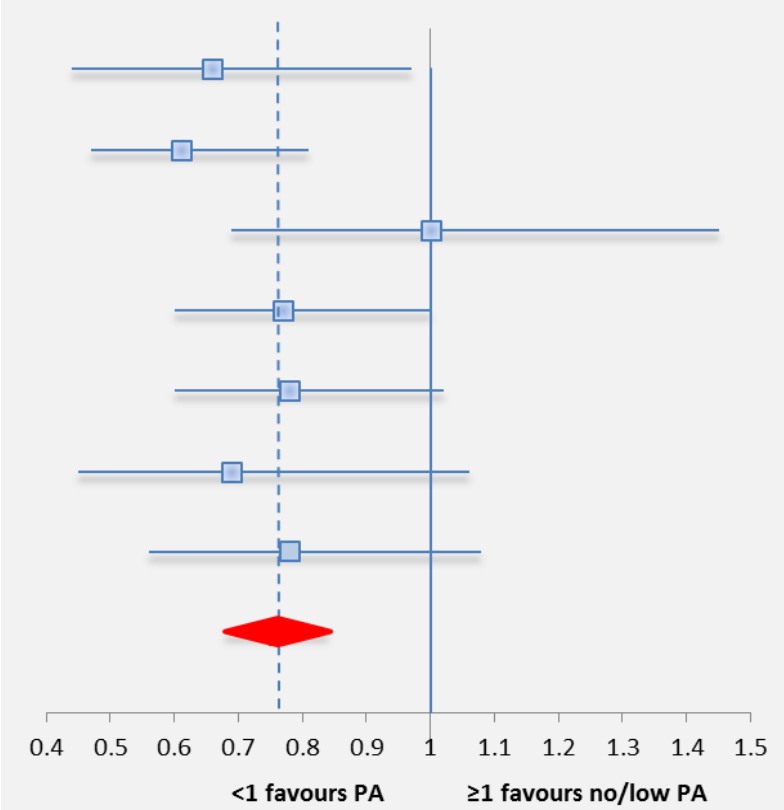
Study	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Cohort/Deaths	Weight (%) random effects analysis
Schmidt et al. 2013		0.66 (0.47 to 0.92)	3393/367	7.97
Irwin et al. 2011		0.61 (0.47 to 0.81)	4643/350	19.63
Hellman et al. 2010		1.00 (0.69 to 1.45)	528/323	9.19
Keegan et al. 2010		0.77 (0.60 to 1.00)	3833/623	23.29
West-Wright et al. 2009		0.78 (0.60 to 1.02)	3539/460	21.00
Irwin et al. 2008		0.69 (0.45 to 1.06)	933/115	6.66
Abrahamson et al. 2006		0.78 (0.56 to 1.08)	1264/290	12.26
Overall		**0.75 (0.68 to 0.84)**	**18133/2506**	**100.00**
Random effects model (I^2=-21.65%)				

Figure 2.7.3 Forest plot with random effects overall hazard ratio for association between **recent (1-3 y) pre-diagnosis recreational physical activity** (highest vs. lowest physical activity categories) and **all-cause death** in breast cancer survivors

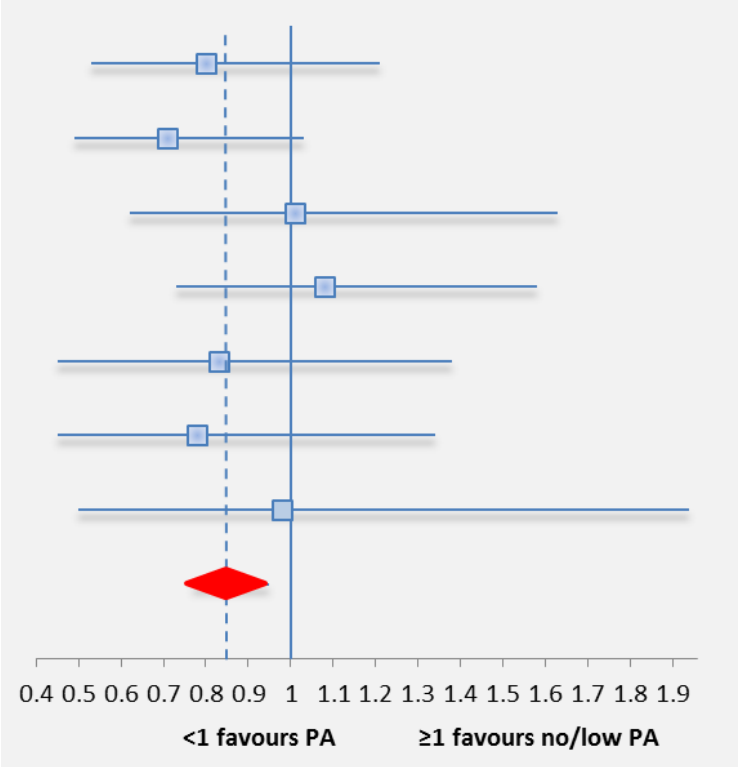
Study	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Cohort/Deaths	Weight (%) random effects analysis
Schmidt et al. 2013		0.80 (0.53 to 1.21)	3393/243	17.38
Irwin et al. 2011		0.71 (0.49 to 1.03)	4643/194	33.39
Hellman et al. 2010		1.01 (0.62 to 1.63)	528/323	8.97
West-Wright et al. 2009		1.08 (0.73 to 1.58)	3539/221	25.39
Irwin et al. 2008		0.83 (0.49 to 1.38)	933/115	5.56
Enger and Bernstein, 2004		0.78 (0.45 to 1.34)	717/251	6.02
Rohan et al. 1995		0.98 (0.50 to 1.94)	412/112	3.29
Overall		**0.87 (0.76 to 0.99)**	**14165/1314**	**100.00**
(I^2=-88.85%)				

Figure 2.7.4 Forest plot with random effects overall hazard ratio for association between **recent (1-3 y) pre-diagnosis recreational physical activity** (highest vs. lowest physical activity categories) and **breast cancer-related death** in breast cancer survivors

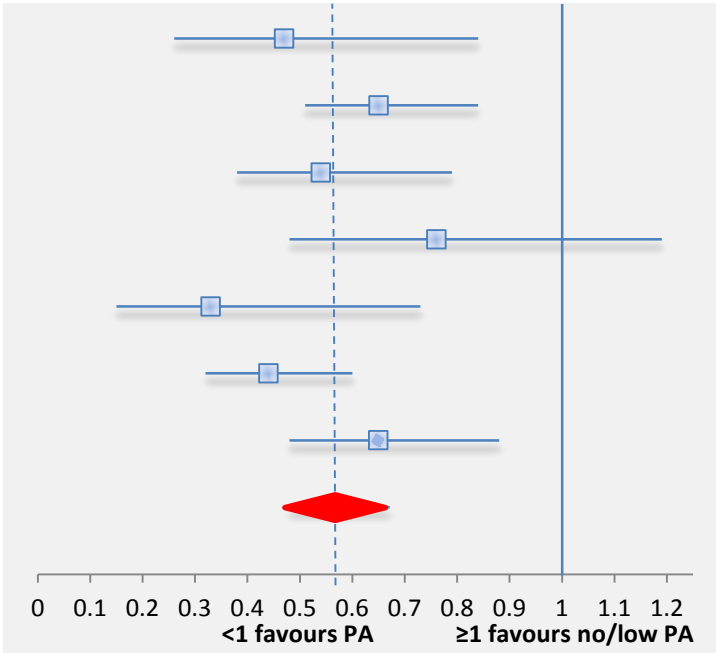
Study	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Cohort/Deaths	Weight (%) random effects analysis
Cadmus Bertram et al. 2011		0.47 (0.26 to 0.84)	2361/163	7.10
Chen et al. 2011		0.65 (0.51 to 0.84)	4826/436	24.60
Irwin et al. 2011		0.54 (0.38 to 0.79)	2910/186	15.11
Sternfield et al. 2009		0.76 (0.48 to 1.19)	1970/187	10.89
Irwin et al. 2008		0.33 (0.15 to 0.73)	688/53	4.14
Holick et al. 2008		0.44 (0.32 to 0.60)	4482/412	18.63
Holmes et al. 2005		0.63 (0.48 to 0.81)	2987/463	19.53
Overall		**0.58 (0.45 to 0.64)**	**20224/1900**	**100.00**
Random effects model (I^2=27.28%)				

Figure 2.7.5 Forest plot with random effects overall hazard ratio for association between **post-diagnosis recreational physical activity** (highest vs. lowest physical activity categories) and **all-cause death** in breast cancer survivors

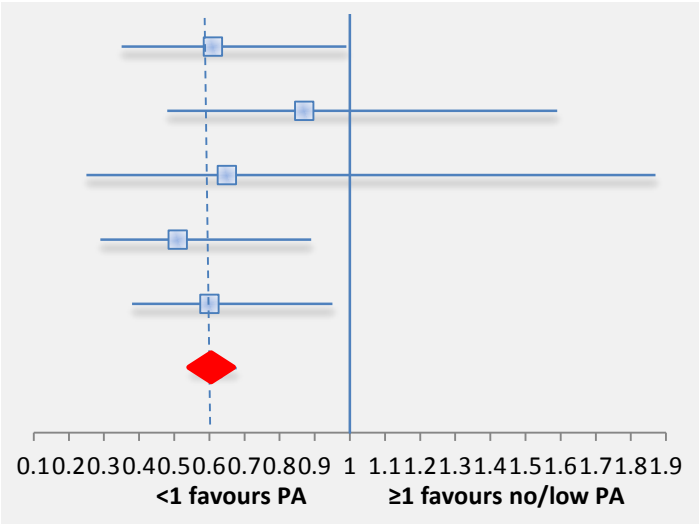
Study	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Cohort/Deaths	Weight (%) random effects analysis
Irwin et al. 2011		0.61 (0.35 to 0.99)	2910/86	15.01
Sternfield et al. 2009		0.87 (0.48 to 1.59)	1970/102	7.03
Irwin et al. 2008		0.65 (0.25 to 1.87)	688/30	9.58
Holick et al. 2008		0.51 (0.29 to 0.89)	4482/109	1.42
Holmes et al. 2005		0.60 (0.38 to 0.95)	2987/280	66.96
Overall		**0.61 (0.55 to 0.68)**	**15015/916**	**100.00**
Random effects model (I^2= -132.34%)				

Figure 2.7.6 Forest plot with random effects overall hazard ratio for association between **post-diagnosis recreational physical activity** (highest vs. lowest physical activity categories) and **breast cancer-related death** in breast cancer survivors

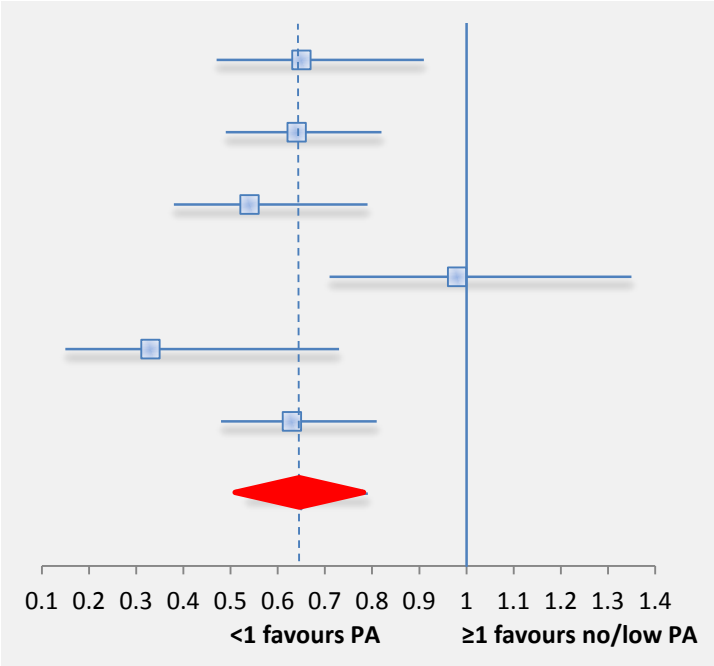
Study	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Cohort/Deaths	Weight (%) random effects analysis
Cadmus Bertram et al. 2011		0.65 (0.47 to 0.91)	2361/163	17.56
Chen et al. 2011		0.64 (0.49 to 0.82)	4826/436	21.80
Irwin et al. 2011		0.54 (0.38 to 0.79)	2910/186	15.79
Sternfield et al. 2009		0.98 (0.71 to 1.35)	1970/187	18.05
Irwin et al. 2008		0.33 (0.15 to 0.73)	688/53	5.25
Holmes et al. 2005		0.63 (0.48 to 0.81)	2987/463	21.54
Overall		**0.62 (0.50 to 0.74)**	**15742/1488**	**100.00**
Random effects model (I^2=50.51%)				

Figure 2.7.7 Forest plot with random effects overall hazard ratio for association between **post-diagnosis meeting recommended physical activity guidelines** (meeting vs. not meeting physical activity guidelines) and **all-cause death** in breast cancer survivors

Table 2.7.4 Summary of random effects overall hazard ratios (HR) and 95% confidence intervals (95% CI) for association between physical activity variables and death in breast cancer survivors

Physical activity (PA) variable	Outcome	HR (95% CI)	Cohort/deaths	I^2
Lifetime recreational pre-diagnosis PA	All-cause death	0.81 (0.68-0.93)	14186/2768	42.1%
	Breast cancer-related death	0.77 (0.57-1.04)	9806/1576	69.8%
Recent (1-3 y) pre-diagnosis recreational PA	All-cause death	0.75 (0.68-0.84)	18133/2506	21.7%
	Breast cancer-related death	0.87 (0.76-0.99)	14165/1314	88.9%
Post-diagnosis recreational PA	All-cause death	0.58 (0.45-0.64)	20224/1900	27.3%
	Breast cancer-related death	0.61 (0.55-0.68)	15015/916	132.4%
Post-diagnosis meeting recommended PA guidelines	All-cause death	0.62 (0.50-0.74)	15742/1488	51.5%

Publication bias

Publication bias was difficult to describe because of the relatively small number of studies included in the current meta-analysis (figure 2.7.8 is presented as an example below; for remaining funnel plots see appendix E). Visual inspection of funnel plot did not suggest publication bias for lifetime recreational physical activity and all-cause death and recent pre-diagnosis recreational physical activity and breast cancer-related death funnel plots as the studies were distributed symmetrically (i.e. inverted funnel shape) about the summary effect size. There was a suggestion of publication bias for lifetime recreational physical activity and breast cancer-related death as there were studies with markedly different effect estimates. However, there was a lack of high precision studies for this comparison and lower precision studies were scattered along the bottom

of the graph, which suggests that publication bias may not be a plausible explanation for funnel plot asymmetry.

There were asymmetrical distributions about the summary effect size for recent pre-diagnosis recreational physical activity and all-cause death, post-diagnosis recreational physical activity and breast cancer-related death and achieving recommended physical activity guidelines post-diagnosis and all-cause death funnel plots. This was due largely to a lack of smaller, less precise studies in the bottom corners of each plot, suggesting the possibility of “missing” studies. However, all of the more precise studies suggested a beneficial effect. For both post-diagnosis recreational physical activity and all-cause death and post-diagnosis recreational physical activity and breast cancer-related death there were no studies showing no effect, which could represent either ‘missing’ less precise studies or a “true” beneficial effect.

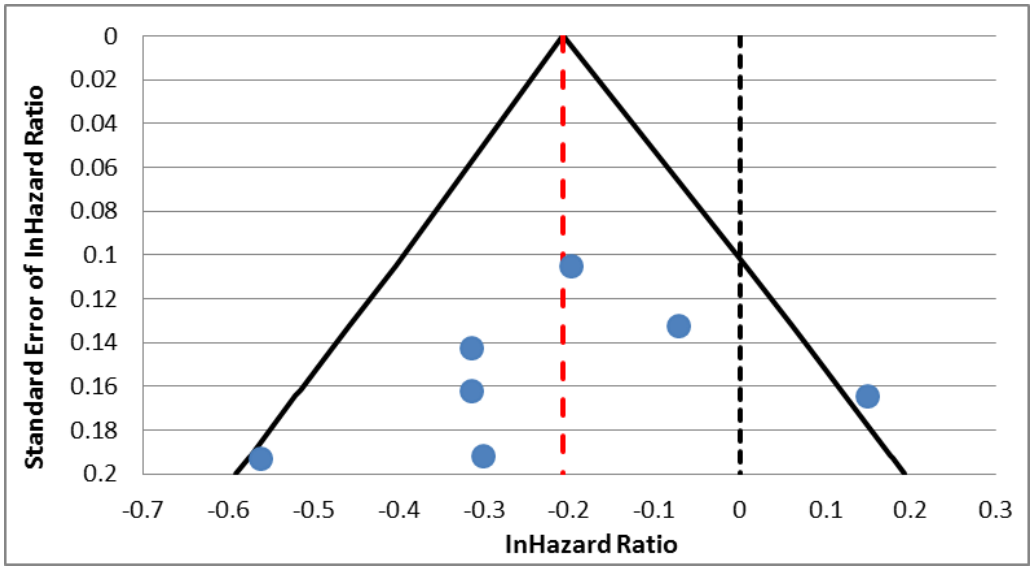


Figure 2.7.8 Lifetime pre-diagnosis recreational physical activity and all-cause death and funnel plot with 95% CI provided (black diagonal lines). Line of no effect is shown as a black dashed line and the effect estimate line is shown as a red dashed line.

2.7.5 DISCUSSION

Of the 21 included prospective cohort and case-control studies, 12 of the studies measured only pre-diagnosis physical activity, nine studies included only post-diagnosis and two studies investigated both pre-diagnosis and post-diagnosis physical activity. We used HRs and 95% CI (HR <0.9 and upper limit 95% CI <1) to determine significant risk reductions. Concerning the role of pre-diagnosis lifetime physical activity, we found significant risk reductions in all-cause death for recreational physical activity in two studies (out of 7) and for moderate-intensity physical activity in one study (out of three). Significant risk reductions in breast cancer-related death was found for lifetime recreational physical activity in one study (out of 5), moderate-intensity lifetime physical activity in two studies (out of 4) and vigorous-intensity lifetime physical activity in one study (out of 3). Two studies reported a statistically significant reduction in breast cancer events risk when comparing the highest versus the lowest moderate-intensity lifetime recreational physical activity. Two studies found a significant dose-response relationship between lifetime recreational physical activity and all-cause death and breast cancer-related death.

In regards to recent pre-diagnosis physical activity, significant reductions in risk of all-cause death were reported for total recreational physical activity in two studies (out of 6) and for moderate-intensity physical activity in one study (out of 1). One study (out of 7) reported significant risk reductions in breast cancer-related death for recent pre-diagnosis recreational physical activity, one study found recent pre-diagnosis moderate physical activity (out of 2), and one study (out of 1) also found

risk reductions for recent pre-diagnosis vigorous-intensity physical activity. Two studies found a significant dose-response relationship between recent recreational physical activity and all-cause death and breast cancer-related death.

When considering the role of post-diagnosis physical activity, six studies out of seven reported significant reductions in all-cause death for recreational physical activity, two studies (out of 3) with moderate-intensity recreational physical activity and five studies (out of 6) for adherence to recommended physical activity guidelines. Significant reductions in breast cancer-related death were found in three studies (out of 5) for post-diagnosis recreational physical activity, while one study (out of 3) found significant risk reductions in those participants meeting recommended physical activity guidelines. Significant risk reductions were found in a study combining breast cancer-related deaths and recurrences with post-diagnosis recreational physical activity. A significant dose-response relationship between total post-diagnosis recreational physical activity and all-cause death and breast cancer-related death was found in seven studies (out of 7) and three studies (out of 5), respectively.

Sub-analyses from individual studies produced conflicting results. For pre-diagnosis physical activity, one study found significant reductions in all-cause death and breast cancer-related death in only post-menopausal breast cancer patients, while no consistent differential effect of physical activity was found between BMI categories or between ER-positive and ER-negative breast cancer. For post-diagnosis physical activity, we found slightly stronger effect of physical activity on risk all-cause and breast

cancer-related death in breast cancer patients with BMI <25 kg·m^2, greater breast cancer-related death risk reductions in breast cancer patients diagnosed with more advanced or regional breast cancer compared to early stage or local breast cancer and greater risk reducing effect on all-cause death in breast cancer patients with ER-negative and/or PR-negative breast cancer.

The results of the meta-analysis suggest that higher levels of lifetime pre-diagnosis physical activity are significantly associated with a reduction in the risk of all-cause death (19% risk reduction) but this association was of borderline significance for risk of breast cancer-related death. Significant reductions in the risk of all-cause death (25%) and breast cancer-related death (13%) were found with recent pre-diagnosis recreational physical activity. Post-diagnosis recreational physical activity was associated with significant reductions in both all-cause (42%) and breast cancer-related death (39%), while breast cancer survivors meeting current recommended physical activity guidelines was associated with significant reductions in risk of all-cause death (38%). However, substantial heterogeneity (i.e. >50%) was found for associations between risk of all-cause death and meeting recommended physical activity guidelines, and for risk of breast cancer-related death and lifetime and recent pre-diagnosis recreational physical activity and post-diagnosis recreational physical activity.

Previous meta-analyses (Beasley et al., 2012; Ibrahim and Al-Homaidh, 2011), which consist of many of the prospective cohort studies included in this current study, support the positive role of physical activity on breast cancer outcomes and are in agreement with the findings of the current

review. A meta-analysis of six studies found an 18% reduction in the risk of all-cause but no reduction in risk of breast cancer-related death with pre-diagnosis physical activity, while post-diagnosis physical activity was associated with 41% and 34% reductions in all-cause death and breast cancer-related death, respectively, and a reduction in breast cancer recurrence of 24% (Ibrahim and Al-Homaidh, 2011). A pooled analysis of four studies, which were all part of the current study, found that post-diagnosis physical activity of at least 10 MET-h·wk^{-1} was associated with similar reductions in the risk of all-cause and breast cancer-related death (27% and 25%, respectively), but found no reduction in breast cancer recurrence risk (Beasley et al., 2012).

The stronger risk reductions in all-cause death associated with physical activity was unsurprising, given the evidence regarding the role of physical activity in reducing the risk of CVD (Kodama et al., 2013; Wen et al., 2011; Myers, 2003), which is the major cause of death in women worldwide (WHO, 2013). Furthermore, a recent cohort study reported a significant association between poor physical health (characterised by obesity and physical inactivity) and all-cause mortality and shorter time to additional breast cancer events (Saquib et al., 2011).

The biological mechanism for the reductions in the risk of breast cancer outcomes associated with physical activity is unknown, but is likely to be similar to the mechanisms thought to reduce the risk of first primary breast cancer. Namely, physical activity may reduce the risk of breast cancer outcomes by reducing adiposity, improving insulin sensitivity, reduced exposure to sex hormones, increased levels of adipokine and decreased

concentration of inflammatory markers (Friedenreich et al., 2010). Stronger risk reductions in breast cancer outcomes with post-diagnosis physical activity may be associated with effects of physical activity on the above biological factors in postmenopausal women, who constitute the majority of breast cancer survivors in these studies. However, it should also be noted that because participants had a lesser duration in which to recall post-diagnosis physical activity, the accuracy of this physical activity may be better than that of pre-diagnosis physical activity.

From visual inspection of the funnel plots, there was a suggestion of publication bias for recent pre-diagnosis recreational physical activity and all-cause death, post-diagnosis recreational physical activity and breast cancer-related death and achieving recommended physical activity guidelines post-diagnosis and all-cause death funnel plots. Publication bias could have influenced the results of the current review and analysis. Although it is important to note that funnel plot asymmetry can result from reasons other than publication bias, such as selective outcome reporting, poor methodological quality leading to inflated effects in smaller less precise studies, true heterogeneity (i.e. size of effects differs according to study size, different populations or differing intensities of intervention), artefactual (i.e. where sample variation leads to an association between the effect estimate and its SE) and random error (i.e. chance).

The inclusion of only published studies in this review and meta-analysis could have increased the risk of publication bias. In addition to this, we searched only one electronic database. Unpublished studies, such as abstract or reports, often report smaller treatment effects (Hopewell et al.,

2007), however, these types of studies are often of poor quality and may not provide sufficient data for pooled or meta-analysis. To minimise the risk of missing possibly relevant studies we carefully examined all relevant meta-analysis and systematic reviews, including three recent reviews (Beasley et al., 2012; Ellsworth et al., 2012; Ibrahim and Al-Homaidh, 2011). We were not aware of any relevant unpublished studies when this current study was conducted. Only studies published in the English language were included, which could have led to an increased risk of language bias. Although the exclusion of non-English language studies might result in smaller effect estimates, language bias is generally small (Juni et al., 2002). Researchers who abstracted and reviewed the data in this current study were not blinded to authors, institutions and journals. However, this may only introduce a small risk of bias, and requires a large amount of administration time (Berlin, 1997).

Substantial heterogeneity was found in several comparisons, including lifetime pre-diagnosis physical activity and meeting recommended physical activity guidelines, and risk of all-cause death and recent pre-diagnosis recreational physical activity and post-diagnosis recreational physical activity and risk of breast cancer-related death. Due to the small number of studies available, subgroup analyses was not possible. Therefore, the results of these comparisons should be treated with caution. This heterogeneity may have resulted from the variation in the methods of the included studies.

In this current study for each comparison made we used the highest and the lowest physical activity categories. However, there was a variation in

how each study categorised the highest and lowest physical activity categories. Therefore, the strength of the association between the physical activity variables and breast cancer outcomes may be dependent on these cut-off points. Furthermore, physical activity outcomes were assessed differently across studies, which make comparisons between studies difficult. For lifetime physical activity some of the studies asked participants to recall physical activity performed over their entire lifetime up to the time of breast cancer diagnosis or one-year pre-diagnosis, while others collected physical activity data from specific age ranges pre-diagnosis. Recent pre-diagnosis physical activity was assessed from one year to three years prior to diagnosis, while post-diagnosis physical activity data was taken from six months to six years after diagnosis and participants were required to recall physical activity during different duration's post-diagnosis.

All studies assessed physical activity using either questionnaires or interviews. Both of these methods are known to be prone to biases, due mainly to recall errors and social desirability (Prince et al., 2009). Validation of these questionnaires is disputed and is difficult to establish due to a lack of a current gold standard criterion method for measuring habitual physical activity (Helmerhorst et al., 2012). Often physical activity questionnaires are validated against accelerometer data which itself has questionable validity. In addition to this, most of the physical activity data related to moderate and vigorous-intensity physical activity, but not low-intensity physical activity. As result, only a small fraction of an individual's physical activity may be measured in a given study, possibly leading to

misclassification of some participants within studies. Moreover, studies varied in the information on types of activities requested from participants.

Observational studies provide insights into aetiology and allow us to make associations between certain factors and disease. However, these types of studies are not able to establish direct, casual links between physical activity and breast cancer outcomes (Carlson and Morrison, 20009). There are currently no RCTs available that have examined physical activity and all-cause death, breast cancer-related death and recurrence in breast cancer survivors. The on-going DIANA (Diet and Androgens)-5 randomized controlled trial of the effectiveness of a Mediterranean diet and moderate physical activity in reducing additional breast cancer events in women with early stage invasive breast cancer at high risk of recurrence because of metabolic or endocrine milieu, may provide important information regarding the effects of diet and exercise on breast cancer outcomes (Villarini et al., 2012). However, RCTs are needed that can isolate the effects of physical activity on breast cancer outcomes.

2.7.6 CONCLUSIONS

There were significant associations between lifetime and recent pre-diagnosis recreational physical activity and risk of all-cause death and recent pre-diagnosis recreational physical activity and risk of breast cancer-related death. Post-diagnosis physical activity was found to significantly reduce the risk of both all-cause death and breast cancer-related death. One study each found a significant reduction in breast cancer recurrences with pre-diagnosis lifetime and recent physical activity, while another study found significant reductions in recurrences and breast

cancer-related deaths combined with post-diagnosis physical activity. However, effect estimates for association between all-cause death and adherence to recommended physical activity guidelines, and breast cancer-related death and lifetime and recent pre-diagnosis physical activity and post-diagnosis recreational physical activity should be treated with caution due to evidence of substantial heterogeneity. Future studies are needed to elucidate the mechanisms by which physical activity may improve survival among breast cancer survivors. There is a need for RCT investigating the role of physical activity on all-cause death and breast cancer outcomes. This current review provides evidence to support the role of physical activity and in particular recent pre-diagnosis and post-diagnosis physical activity in potentially improving and extending overall survival after a diagnosis of breast cancer.

2.8 Physical activity for women with breast cancer after adjuvant therapy; systematic review and meta-analysis of Interventions

This systematic review is currently in the protocol stage of being written up as a Cochrane systematic review.

2.8.1 ABSTRACT

Background: Recent observational and trial evidence suggests that physical activity may reduce mortality and improve physical and psychological function in breast cancer survivors. Physical activity prescriptions for breast cancer survivors rely on evidence as to whether activity during or after treatment results in improved health outcomes. Therefore, the aim of this study was to assess the effects of physical activity interventions in post-adjuvant therapy breast cancer survivors.

Methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 10), and the following electronic databases: MEDLINE (1966 to October 2012), EMBASE (1980 to October 2012), PsychINFO (1872 to October 2012), Global Health (1973 to October 2012), Health Management Information Consortium (1979 to October 2012), CINAHL (1937 to October 2012), PeDRO (1929 to October 2012) and SPORT Discus (1975 to October 2012), OPENGrey (1880 to October 2012), ProQuest Dissertations and Theses (1861 to October 2012) and Conference Papers and Proceedings Index (1973 to October 2012), and the Web of Knowledge Citation databases, Science Citation Index Expanded (1970 to October 2012), Social Sciences Citation Index (1970 to October 2012), Arts and Humanities Citation Index (1975 to October 2012), and Conference

Proceedings Citation Index of Science (1990 to October 2012) and Social Science (1990 to October 2012). In addition to this, we screened references in relevant reviews and clinical trials and handsearched relevant journals. We included randomised and non-randomised controlled trials that examine interventions aimed effects of physical activity interventions in breast cancer survivors after adjuvant therapy. The researcher extracted data and assessed the adequacy of the trials. Study authors were contacted for further information if necessary.

Results: We included 34 trials with a total of 3,051 participants randomised to the physical activity intervention (n = 1,720) or the comparison (n = 1,319) groups. All trials consisted of stage 0-III breast cancer patients who had completed all active treatment except hormone therapy. Mode of the physical activity intervention differed across trials and included aerobic exercise (walking, cycling, step-aerobics or a variety of aerobic activities), resistance training, aerobic and resistance exercise combined, Greek dance, yoga and Tai Chi. Outcome measurements included physical activity levels, cardiorespiratory fitness, anthropometric measurements, HRQoL outcomes, fatigue, psychological health outcomes, blood biomarkers and bone health-related outcome measures.

The results suggest that physical activity interventions compared with control interventions have a significant positive impact on physical activity levels (assessed by questionnaire), cardiorespiratory fitness, BMI, body fat percentage (%), lower and upper body strength, systolic blood pressure at rest, general health-related quality of life (HRQoL), physical and mental/emotional well-being, fatigue, self-esteem, depression, anxiety,

Insulin-like Growth Factor (IGF)-Binding Protein 3 (IGF-BP3) and interferon-γ. No significant effect of physical activity was found for accelerometer-derived physical activity levels, mass, lean mass, waist and hip circumferences, waist-hip ratio (WHR), sleep disturbance, plasma insulin, glucose, Homeostatic Model Assessment (HOMA), High-density Lipoprotein, triglycerides, IGF-1 or IL-6. There was insufficient number of trials with common bone-related outcome measures to be included in the meta-analysis and results reported in these trials were inconsistent.

The effect of physical activity on outcome measures differed according to the mode of exercise, the instruments used to assess the various outcomes, the presence of a psychological support component. Aerobic exercise only interventions compared with controls had a positive effect on physical activity levels (both questionnaire and accelerometer-derived), cardiorespiratory fitness, upper body strength, general HRQoL, physical and mental/emotional well-being and depression. While aerobic and resistance exercise combined trials suggested positive effects on mass, BMI, general HRQoL, physical well-being, fatigue, depression and anxiety. Resistance training exercise trials improved upper and lower body strength significantly. The measurement instrument used influenced the effects of physical activity compared to controls on physical activity level, cardiorespiratory fitness, body fat %, general HRQoL, mental/emotional well-being and fatigue. Trials with a psychological support component suggested that physical activity interventions with this component can positively affect physical activity levels (assessed by questionnaire), cardiorespiratory fitness, mass, BMI, body fat %, upper body strength,

general HRQoL, physical and mental/emotional well-being, self-esteem and depression compared to controls.

Results of the review need to be interpreted cautiously owing to the risk of bias and heterogeneity of the interventions assessed and the measurements instruments used across studies. All the trials reviewed were at high risk for performance bias. In addition, the majority of trials were at high risk for attrition bias and at a high or unclear risk of detection and selection bias.

Conclusions: This systematic review indicates that physical activity may have beneficial effects on physical activity levels (assessed by questionnaire), cardiorespiratory fitness, BMI, body fat %, lower and upper body strength, systolic blood pressure at rest, general HRQoL, physical and mental/emotional well-being, fatigue, self-esteem, depression, anxiety, IGF-BP3 and interferon-γ. The positive results must be interpreted cautiously due to the heterogeneity of physical activity interventions assessed, measurement instruments used to assess the various outcomes and the risk of bias in many trials. Further research is required to investigate how to sustain positive effects of physical activity over time and to determine optimal prescription of physical activity (mode, intensity, frequency and duration) for breast cancer survivors. In addition, there is currently a lack of research regarding the effects of physical activity in ethnic populations of breast cancer survivors.

2.8.2 BACKGROUND

Worldwide, breast cancer is the most frequently diagnosed cancer and a leading cause of cancer death among females, accounting for 23% (1.38 million) of the total cancer cases and 14% (458,400) of the cancer deaths in 2008 (Jemal et al., 2011). Of newly-diagnosed cases of cancer in the UK during 2006-08, breast cancer had the highest incidence rate of all cancers in females (46,840 cases or 123 cases per 100,000 females) and was the second highest cause of death from cancer in females (12 122 deaths or 25.9 deaths per 100,000 females). Despite improved one-year and five-year mortality rates for women with breast cancer, the incidence of breast cancer is projected to rise by 44% (22% due to risk increase and 21% due to population change) by 2020 (Moller et al., 2007). Many women still die as a result of breast cancer and given the projected increases in breast cancer incidence, it is important that interventions are explored that can improve both the survival rates of women diagnosed with breast cancer and the quality of life of those living with breast cancer.

Due to the increasing incidence of breast cancer and improved survival rates, there has been an increased attention to tertiary prevention among women with breast cancer. In addition to the risk of a cancer recurrence, breast cancer patients often experience numerous short- and long-term disease- or treatment-related adverse physiologic and psychosocial outcomes, such as cardiotoxicity, neurotoxicity, secondary leukaemia, lymphedema, premature menopause, sexual dysfunction, infertility, weight gain, difficulty sleeping and fatigue (Azim et al., 2011; Bovelli et al., 2010; de Jong et al., 2002; Beisecker et al., 1997). These adverse effects would be expected to result in a negative impact on HRQoL and physical

function. In addition, these unwanted effects can be prolonged after the completion of active treatment and hinder the patients' return to normal life (Fong et al., 2012).

Physical activity (any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level) and exercise (planned, structured and repetitive physical activity, aimed at improving/maintaining one or more component of physical fitness) represents a modifiable health behaviour that could alleviate the sequelae related to breast cancer and assist patients in returning to the health status they had prior to treatment (Physical Activity Guidelines Advisory Committee Report, 2008). Evidence suggests that higher levels of post-diagnosis physical activity in breast cancer survivors can significantly reduce the risk of dying from breast cancer and/or all-causes (Cadmus Bertram et al., 2011; Chen et al., 2011; Irwin et al., 2011; Holick et al., 2008; Irwin et al., 2008; Holmes et al., 2005). Increased physical activity is associated with reduced exposure to oestrogen and androgens and increased concentrations of SHBG, improved insulin sensitivity and decreased concentrations of IGF-1 and adipokines and other inflammatory markers, with the exception of a beneficial elevation in adiponectin concentrations (Lynch et al., 2011). In addition to the above, a recent study (Santos et al., 2014) has observed, using in-vitro and in-vivo methods, that LDL-C promotes cell proliferation through overexpression of HER2 and migration and decreased expression of cadherin-related family members, both hallmarks of the epithelial to mesenchymal transition implicated in metastasis. Physical activity can lower LDL-C concentrations and positively influence HDL-C concentrations and therefore, potentially

lower the risk of breast cancer events. The effects of increased physical activity outlined above may provide the mechanisms that explain the associated reductions in all-cause and breast cancer-related mortality. Furthermore, a lack of physical activity has been shown to relate to weight gain post-breast cancer diagnosis, which has in turn been linked to poorer survival in some studies (Kroenke et al., 2005; Camoriano et al., 1990). More active women have been found to possess a lower BMI and were less likely to have gained weight after diagnosis, thus improving their survival chances (Holmes et al., 2005; Lahmann et al., 2005).

In a recent meta-analysis, physical activity was associated with important positive effects on physical functions, body mass, BMI and both physical and social functioning domains of HRQoL in patients who had completed their treatment for cancer (Fong et al., 2012). There is evidence to suggest that physical activity can facilitate positive physiological and psychological benefits in cancer survivors during and after treatment (Galvao et al., 2005; Ingram and Visovsky, 2007; Knols et al., 2005; Schmitz et al., 2005). The results from a recent Cochrane review, indicated that physical activity may have beneficial effects on overall HRQoL and certain HRQoL domains including cancer specific concerns (e.g. breast cancer), body image/self-esteem, emotional well-being, sexuality, sleep disturbance, social functioning, anxiety, fatigue and pain at varying follow-up periods (Mishra et al., 2012).

Despite the proposed benefits of physical activity, there is a lack of a consensus regarding the most effective delivery mode and prescription of physical activity in this population. Physical activity interventions are

typically delivered under supervised conditions (Littman et al., 2012; Milne et al., 2008) or under self-directed, home-based conditions (Pinto et al., 2008; Matthews et al., 2007; Vallance et al., 2007). They consist of a comparison between either solely or a combination of aerobic exercise training (Courneya et al., 2003; Herrero et al., 2006; Hutnick et al., 2005), walking (Matthews et al., 2007), and/or resistance training (Schmitz et al., 2009; Schmitz et al., 2005) and standard or usual care. Their duration can vary from less than 10 weeks (Fillion et al., 2008; Daley et al., 2007) to up to 12 months (Saarto et al., 2011; Schmitz et al., 2009).

Previous systematic reviews and meta-analyses have either included studies involving all cancer patients (Brown 2012; Fong 2012; Mishra 2012a; Mishra 2012b; Cramp 2010; Knols 2010; Speck 2010) rather than those only consisting of breast cancer patients, have studied cancer patients receiving adjuvant therapy (Carayol 2013; Mishra 2012b; Markes 2009; McNeely 2006), have focused only on a particular physical activity mode, such as walking (Knols 2010), yoga (Cramer 2013), dance (Bradt 2011) and resistance training (Cramp 2010; Cheema 2008) or have investigated only a particular outcome, such as HRQoL (Cramp 2010; Mishra 2012a; Mishra 2012b) and upper-limb dysfunction (McNeely 2010). Therefore, there is a need for a systematic review and meta-analysis investigating the effects of physical activity on the large range of outcomes reported in trials including post-adjuvant therapy breast cancer patients.

OBJECTIVE(S)

To assess the effects of physical activity interventions for women with breast cancer after adjuvant therapy

2.8.3 METHODS

2.8.3.1 Criteria for considering studies for this review

Types of studies

All RCTs investigating the effects of physical activity interventions for female breast cancer patient's post-adjuvant therapy were included. Quasi-randomized controlled trials and controlled clinical trials will also be considered for inclusion in this review.

Types of participants

Studies including women of all ages diagnosed with breast cancer were reviewed. Studies including cancers other than breast cancer were excluded unless separate data were available for the breast cancer subgroup. Studies including patients with metastatic breast cancer (stage IV and above breast cancer) were excluded. Studies including patients undergoing adjuvant therapy (radiotherapy, biological therapy and chemotherapy but not endocrine therapy) for breast cancer during the exercise intervention were also excluded.

Types of interventions

Interventions in which physical activity/exercise was promoted and/or measured as an outcome and/or its effects assessed were included. We excluded studies with an additional treatment arm or combined intervention (e.g. exercise with diet modification) where the effects of exercise could not be isolated, trials of single exercise sessions that measured acute effects, trials investigating effects of physiotherapy and trials restricted to stretching or local muscular endurance (e.g. training of

shoulders, back/legs only) or therapeutic exercise regimens addressing only specific impairments related to the shoulder, arm or both.

Types of outcome measures

Outcome measures did not form part of the criteria for including studies in a review. All outcomes assessed in relevant studies were included. It was expected that the amount of outcomes would be broad and not all directly related to breast cancer, therefore, it was an aim of the review to highlight the need for agreement between researchers regarding relevant outcomes in breast cancer and physical activity studies.

Expected primary outcomes:

- Physical activity, defined as any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level, and measured by self-report via questionnaires or objectively via accelerometers
- Cardiorespiratory fitness, defined as the ability to engage in physical activities that rely on oxygen consumption as the primary source of energy, and measured either directly or indirectly to obtain an individual's maximal oxygen uptake (VO_2 max)

Expected secondary outcomes:

- Body mass, BMI and body composition (e.g. measures such as body fat percentage, fat-free/lean mass and/or fat mass)
- Other anthropometric measurements (e.g. waist and/or hip circumference and waist-hip ratio, WHR)

- HRQoL, defined as a subjective and multidimensional concept encompassing physical and occupational function, psychological state, social interaction and somatic sensation
- Muscular strength, defined as the maximal force (expressed in newtons, kilograms or pounds) that can be generated by a specific muscle or muscle group
- Blood biomarkers, such as glucose-insulin dynamics, lipid profiles, insulin-like growth factors and inflammatory cytokines
- Bone health-related outcomes such as bone mineral density and bone mineral content
- Adverse events such as musculoskeletal injuries, lymphedema and illness (such as bronchitis and influenza)

2.8.3.2 Search methods for identification of studies

Electronic searches

- The electronic databases, MEDLINE, EMBASE and CENTRAL were searched. The subject-specific electronic databases CINAHL, PsychINFO, PeDRO and Sports Discus were also searched. Citation indexes such as the Science Citation Index and SCOPUS were searched to identify additional studies. Relevant dissertations and theses were searched for on the databases PROQuest and theses.com.

Searching other resources

- A search for relevant grey literature was conducted using the OPENGrey and Healthcare Management Information Consortium (HMIC) and PsycExtra databases.

- After the initial search, key journals were handsearched. Journals were identified and prioritized according to where most of the trial reports appeared based on earlier searches.
- The reference lists of relevant studies, previous relevant reviews and evidence-based guideline papers were scanned for additional relevant studies.
- Key researchers in the subject area were contacted and asked whether they know of any previous studies not identified by this current reviews search or any forthcoming studies they may be aware of.

Full details of the search strategy can be found in the appendix F.

2.8.3.3 Data collection and analysis

Selection of studies

The search results from the searches described above were merged and duplicate records of the same report were removed. The titles and abstracts were examined to remove obviously irrelevant reports. Full texts of potentially relevant reports were retrieved and multiple reports of the same study were linked together. Full text reports were examined for compliance of studies with eligibility criteria. Correspondence with investigators was sought where appropriate to clarify study eligibility or to seek further information, such as missing data. A list of studies that were close to inclusion but after further inspection would not meet criteria was included. Non-English language trials were included and these trials were translated where necessary so that eligibility could be assessed and subsequently data could be extracted. After final decisions on study inclusion were made data collection commenced.

Data extraction and management

A checklist of items to consider in data collection was devised. This checklist included the source of report, confirmation of eligibility or reason for exclusion, methods such as study design, total duration, sequence generation, allocation sequence concealment, blinding, and other sources about bias, participant information such as total numbers, diagnostic criteria, demographic information, and date of study, intervention details, for each outcome of interest the definition, unit of measurement, and scales, results including number of participants allocated to groups, sample size, missing data, summary of data for each group, effect estimates with confidence intervals, and miscellaneous information such as funding sources, key conclusions, and details of any correspondence. Multiple publications for the same trial were collated and the earliest publication was used as the primary reference.

Assessment of risk of bias in included studies

Data collected from the reports were summarized in a “characteristics of included studies” table. The Cochrane collaboration “risk of bias” tool was used to assess possible sources of bias in the included reports (Higgins and Green, 2011). The assessment of risk of bias is a two part tool addressing six specific domains, such as sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting bias and “other issues”. The first part describes what was reported to have happened in a study, while the second part includes the judgment relating to the risk of bias for each domain in that study. If there was evidence of heterogeneity, a large risk of bias and/or low quality of evidence the findings were interpreted cautiously. The assessment of risk of bias was

displayed in a “risk of bias” table. Data tables, forest plots and summary of findings table were used to present the results of the systematic review.

Measures of treatment effect

We originally planned to assess the effects of physical activity on breast cancer outcomes (i.e. rates of survival and recurrence), physical outcomes and psychological outcomes. However, none of the eligible studies provided data on breast cancer outcomes. We anticipated that some outcomes may not be assessed by multiple studies, therefore, we performed a meta-analysis only on an outcome if it was assessed in at least two studies and if outcomes were not too diverse, studies were not at risk of serious bias and if there was no evidence of serious publication or reporting bias. The end of intervention outcome values were used in the analysis in preference to change values or end of follow-up values.

Continuous outcomes (such as cardiorespiratory fitness, physical activity, anthropometric measures, muscular strength, blood biomarkers and bone health-related outcomes) were combined using a weighted mean difference (WMD) when trials measured an outcome using either the same measurement method or scale to generate continuous data. We used a standardized mean difference (SMD) when trials used different instruments to measure the same outcome. The SMDs (or effect sizes) were interpreted as follows: 0.2 and below represented a small effect, above 0.2 to below 0.5 a low to moderate effect, 0.5 a moderate effect, above 0.5 to below 0.8 a moderate to large effect and 0.8 and above a large effect (Cohen, 1998). For dichotomous outcomes (such as adverse events), risk ratios (RR) with 95% confidence intervals (CIs) were used.

Data presented as odds ratios (OR) will be transformed using the method outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins and Green, 2011). For time-to-event outcomes such as mortality and recurrence, hazard ratios (HR) with 95% CI were used. We reported the ratios of treatment effects for response so that a HR less than 1.0 signified a reductive effect on an outcome and a HR greater than 1.0 represented an additive effect on an outcome.

Unit of analysis issues

In the case of trials that have more than one applicable physical activity group and more than one relevant control group, where possible we created a single pair-wise comparison by combining outcome data recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins and Green, 2011).

Dealing with missing data

Missing data were requested from authors. If variability was presented by measures other than standard deviations we obtained *s* using standard approaches for transforming data. We transformed confidence intervals, t values, and *P* values into *s* using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks et al., 2011); when F-statistics were reported for comparing two groups, we transformed F-statistics into t-statistics using the following formula: $t=\sqrt{F}$ and continued transforming the t-statistic into *s*.

Assessment of heterogeneity

For each outcome, we first assessed study heterogeneity with Cochran's Q test (Cochran, 1954), with P<0.10 indicating evidence of heterogeneity. Inconsistency of results across studies was evaluated by the I^2 statistic. I^2 describes the percentage of variability in the point estimates that is due to heterogeneity rather than sampling error (Higgins et al., 2003). Following Higgins and Green (2011), we interpreted I^2 values of 0% to 40% as "might not be important", 30% to 60% as "may represent moderate heterogeneity", 50% to 90% as "may represent substantial heterogeneity" and 75% to 100% as "considerable heterogeneity". However, the importance of the observed value of I^2 was dependent on the magnitude and direction of effects and the strength of evidence for heterogeneity (e.g. P value from the Q test, or a CI for I^2). In addition to the presence of random error (i.e. chance), heterogeneity can result from differences between physical studies after adjuvant breast cancer treatment can also result from real differences between study populations, adjuvant breast cancer treatments received and the training stimulus. The random-effects model considers these additional sources of between-study variability as well as within-study variability.

Assessment of reporting biases

To investigate publication bias, we prepared funnel plots and visually examined them for signs of asymmetry. We followed the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne et al., 2011) for identification of publication bias. Publication bias was deemed to be absent if the funnel plot resembled a symmetrical inverted funnel shape. Publication bias was suspected if there

were studies with markedly different intervention effect estimates, if smaller studies tended to lead to more or less beneficial effect estimates, and if the funnel plot was skewed and asymmetrical (i.e. gaps in bottom right and left corners indicating “missing studies”).

Data synthesis

The pooled intervention effect estimates and their 95% CI were presented. Continuous data were combined using either the inverse-variance fixed-effect method or the inverse-variance random-effects method, depending on the presence of heterogeneity. For RR data a random-effects model (Der Simonian and Laird, 1986) was used to combine data where heterogeneity was suspected, while the fixed-effects Mantel-Haenzel methods (Mantel and Haenzel, 1959; Greenland and Robins, 1985) was used when heterogeneity was not suspected. For HR data, study results were combined using the generic inverse variance method for both random- and fixed effect models. All analyses were carried out using RevMan (version 5.2).

Subgroup analysis and investigation of heterogeneity

We considered the following study characteristics for heterogeneity: mode of physical activity, measurement instrument used and presence of a psychological support component.

Sensitivity analyses

We also conducted a sensitivity analysis to assess the effects of including studies with high risk of allocation bias.

2.8.4 RESULTS

2.8.4.1 Description of studies

Results of the search

Through a comprehensive literature search, 1,519 potentially relevant references were identified and screened for retrieval. After duplicates were removed, a total of 639 references were excluded based on the title and abstract with 349 references retrieved for more detailed evaluation. From these, 96 trials were excluded as they did not meet the inclusion criteria and 34 trials were identified as appropriate for inclusion in the current review (figure 2.8.1).

Included studies

The final selection resulted in 34 trials being included in this review (Bower et al., 2011; Cadmus et al., 2009; Cantarero-Villanueva et al., 2011; Carson et al., 2009; Cho et al., 2006; Courneya et al., 2003; Daley et al., 2007; DeNysschen et al., 2011; Fillion et al., 2008; Heim et al., 2007; Herrero et al., 2006; Hutnick et al., 2005; Kaltsatsou et al., 2011; Ligibel et al., 2008; Littman et al., 2012; Matthews et al., 2007; Mefferd et al., 2007; Mehnert et al., 2011; Milne et al., 2008; Musanti, 2012; Mustian et al., 2004; Niemen et al., 1995; Nikander et al., 2007; Payne et al., 2008; Pinto et al., 2003; Pinto et al., 2005; Rahnama et al., 2010; Rogers et al., 2009; Saarto et al., 2011; Schmitz et al., 2005; Schmitz et al., 2009; Sprod et al., 2010; Vallance et al., 2007; Winters-Stone et al., 2011) (earliest publication of each trial was used as the trial reference). We reviewed and included information on trial characteristics and outcome-related data from an additional 40 publications that were secondary publications to several of the 34 trials. We corresponded with and requested additional data from

seven trial authors, and only one of these trials authors replied to requests for additional data. For trial characteristics and outcomes see the summary characteristics of included studies table (table 2.8.1).

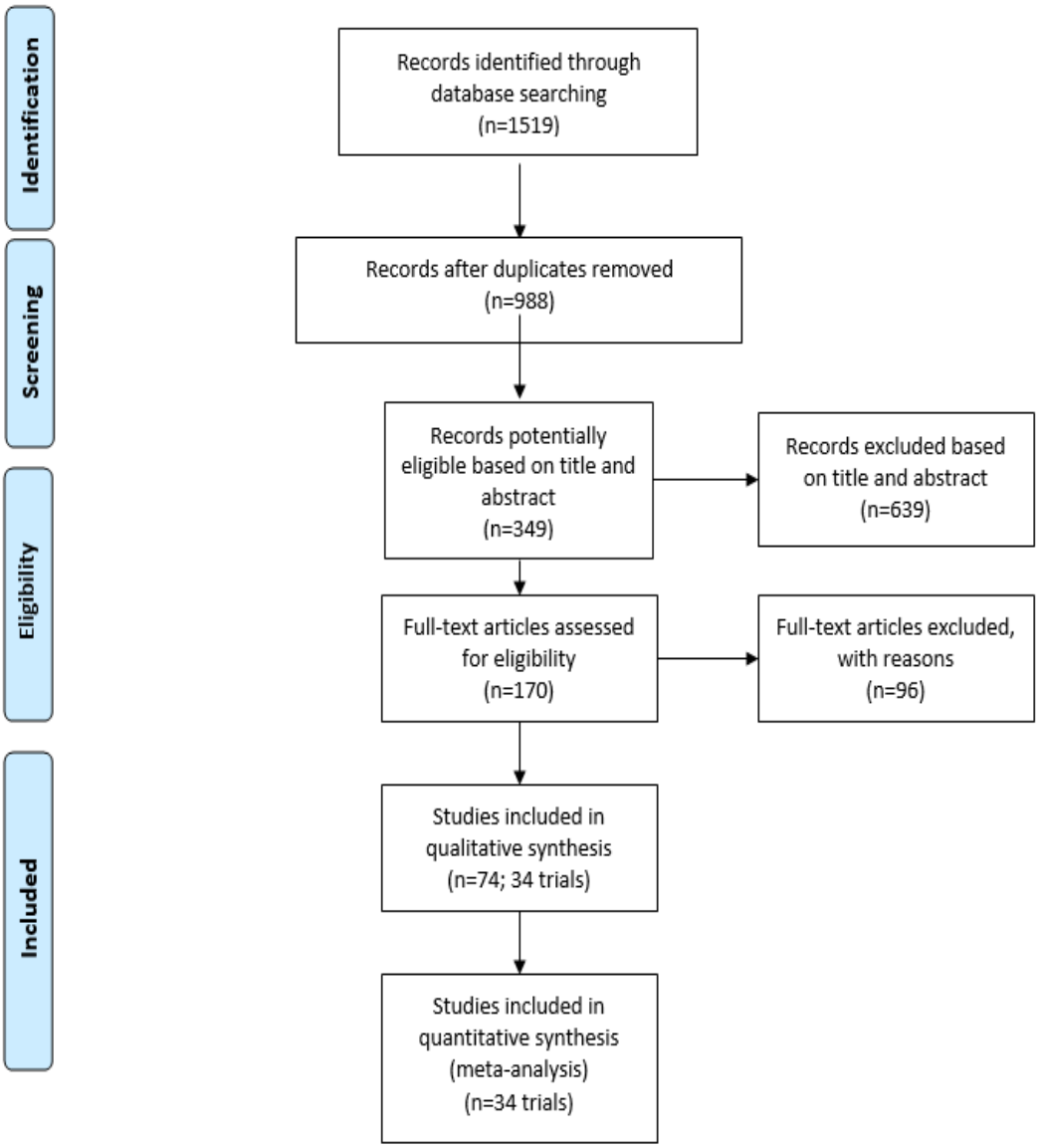


Figure 2.8.1 Selection process of eligible trials for inclusion in review

Table 2.8.1 Summary of characteristics of included studies

Study	Sample N (intervention /control)	Mean age /range (y)	Stage	Mode	Intervention duration	Intervention details	Control group details
Bower et al. 2011	31 (16/15)	54	0-II	Yoga	12 wks	2 x 90 min/wk of Iyengar yoga: postures, breathing techniques	1x120 min health education classes in groups of 4-7
Cadmus et al. 2009	75 (37/38)	56	0-III	Aerobic	6 mo or 12 mo	3-5 x 15-30 min/wk aerobic exercise at 50%, 60%-80% of predicted HRmax (220-age). Supervised 3 days/wk and additional 2 days/wk either at the health club or on their own.	Usual care
Cantarero-Villanueva et al. 2011	78 (38/40)	49	I-III	Aerobic + resistance	8 wks	3 x 60 min/wk of aerobic (intensity not reported) and resistance training, consisting of fit-ball and bodyweight exercises, and resistance bands, at 75% of maximum load for resistance exercises, progression, increase 5% per week. Resistance exercises, 10-12 repetitions x 2-3 sets; 30 s rest in between sets.	Usual care
Carson et al. 2009	37 (17/20)	54	I-II	Yoga	8 wks	1 x 120 min/wk of Yoga of Awareness: yoga postures, breathing techniques, meditation, study of pertinent topics, group discussion	Wait list control
Cho et al. 2006	65 (34/31)	49	I-II	Aerobic	10 wks	2 x 90 min/wk consisting of aerobic exercise at 40%-60 of HRmax. Additional psychology-based education and peer support group activity provided	Wait list control
Courneya et al. 2003	53 (25/28)	59	I-III	Aerobic	15 wks	3 x 15-35 min/wk of aerobic exercise (upright or recumbent cycle ergometer) at 70%–75% VO_2 peak	Wait list control
Daley et al. 2007	108 (34/74)	50	I-III	Aerobic	8 wks	3 x 50 min of moderate exercise (65-85% age predicted HRmax)	Usual care and exercise-placebo
DeNysschen et al. 2011	100 (66/34)	51		Aerobic	4-6 mo	3-5 x 30 min/wk of aerobic exercise at Borg Scale of 12 to 14 level (moderate exertion)	Usual care with telephone calls
Fillion et al. 2008	94 (48/46)	53	0-III	Walking	4 wks	4 x 60 min/wk walking and 1.5 hours of psycho-educative, fatigue management sessions	Usual care

Study	Sample N (intervention /control)	Mean age /range (y)	Stage	Mode	Intervention duration	Intervention details	Control group details
Heim et al. 2007	63 (32/31)		NR	Walking + resistance	Not specified	2 x 30 min/wk of aerobic exercise (walking) 3 x 30 min/wk of resistance training (9 exercises for all large muscle groups). Educational program, physical therapy, group exercise, and psycho-oncologic intervention	Education, physiotherapy, psycho-oncology group
Herrero et al. 2006	20 (10/10)	51	I-II	Aerobic + resistance	8 wks	3 x 90 min/wk of 20-30 min cycling at 70-80% age predicted HRmax and resistance exercise progressively increased intensity of 12-15 repetitions at 12–15 repetition max.	Usual care
Hutnick et al. 2005	49 (28/21)	50	I-III	Aerobic + resistance	6 mo	3 x 40–90 min/wk (20 min Aerobic training: 60–75% functional capacity based on VO_2 max; 4 x upper and lower body resistance exercises: 8–12 repetitions x 1–3 sets)	"Non-exercisers"
Kaltasou et al. 2009	27 (14/13)	57	NR	Greek dance + resistance	24 wks	3 x 60 min/wk (25 min of Greek traditional dances at 65 and 80% of age predicted HRmax. Upper body exercise training and the cool-down lasted 25 min; resistance machines.	Usual care
Ligibel et al. 2008	101 (51/50)	53	I-III	Aerobic + resistance	16 wks	1 x 90 min/wk of aerobic exercise; 2 x 50 min of resistance training	Wait list control
Littman et al. 2012	63 (32/31)	59	0-III	Yoga	6 mo	1-3 x 75 min/wk of Viniyoga: yoga postures, breathing techniques, deep relaxation, meditation	Wait list control
Matthews et al. 2007	36 (23/13)	54	I-III	Walking	12 wks	3–5 x 20–40 min/wk of walking at RPE 11-13 (home-based, unsupervised – +1 x 30 min in-person counselling visit and five brief phone calls over the 12 weeks)	Wait list control
Mefferd et al. 2007	85 (56/29)	56	I-III	Aerobic + resistance	16 wks	7 x 1 h/day of moderate to vigorous physical activity. 2-3 sessions per wk of muscle strengthening exercises (duration or intensity not provided). Participants also attended group sessions covering elements of cognitive behavioural therapy for obesity. Telephone contact was made 4 times in the initial 2 weeks and once weekly	Wait list control
Mehnert et al. 2011	63 (35/28)	52	I-III	Aerobic	10 wks	2 x 90 min/wk of aerobic exercise at 60% VO_2 max	Usual care

Study	Sample N (intervention /control)	Mean age /range (y)	Stage	Mode	Intervention duration	Intervention details	Control group details
Milne et al. 2008	58 (29/29)	55	I-III	Aerobic and resistance	12 wks	3 x 60 min/wk (20 min aerobic and 30 min resistance training: 2 sets of 10-15 repetitions of light weights; progressed to heavier weights once current weight and repetitions were achieved with good form.	Delayed intervention with telephone calls
Musanti 2012	55 (42/13)	51	I-III	Walking, resistance and walking and resistance combined	12 wks	Aerobic exercise group: 3 x 15-30 min/wk walking at 40-65% HRmax, progressing to 85% HRmax; Resistance exercise group: 3 sessions of resistance training per wk at RPE (0-10) 3-5 progressing to 7-8. Aerobic and resistance combined: 4-5 times per week aerobic (15-30 min at 40%-65% and up to 85% HRmax) and 2 times per week resistance (RPE 3-5 then to 7-8).	Flexibility (stretching exercise) control with telephone calls
Mustian et al. 2004	31 (17/14)	52	0-III	Tai Chi Chaun	12 wks	Tai Chi Chuan 3 x 60 min/wk	Supportive expressive group
Niemen et al. 1995	16 (8/8)	56	NR	Walking and resistance	8 wks	3 x 60 min/wk (30 min of walking at 75% maximum intensity plus 30 min of resistance training at 2 sets of 12 repetitions for 7 exercises).	Sedentary control group
Nikander et al. 2007	29 (15/14)	52	I-III	Aerobic	12 wks	1 x supervised and 2–3 x home-based unsupervised exercise for 50-60 min/wk at RPE 11–16 of step aerobics consisted 150 to 180 jumps and leaps and circuit-training consisted of 3 rounds of 8-10 different vigorous movements such as rope-jumping and skate-jumping resulting in a total of 100 to 150 jumps and leaps during each session. In addition to this, home-based circuit training and aerobic exercise.	Usual care
Payne et al. 2008	20 (10/10)	65	NR	Walking	14 wks	4 x 20 min/wk of moderate home-based walking with pedometers	Usual care
Pinto et al. 2003	24 (12/12)	53	0-II	Aerobic	12 wks	3 x 50 min/wk consisting of 30 min of aerobic exercise at 60%-70% HRmax. During the last month, participants performed strength training with light weights for upper body.	Wait list control

Study	Sample N (intervention /control)	Mean age /range (y)	Stage	Mode	Intervention duration	Intervention details	Control group details
Pinto et al. 2005	86 (43/43)	53	0-II	Aerobic	12 wks	2-5 x 10-30 min/wk aerobic exercise at 55%–65% HRmax	Usual care with telephone calls
Rahnama et al. 2010	29 (14/15)	50-65	I-III	Walking and resistance	15 wks	2 x 25-35 min/wk of supervised walking at 45%-65% HRmax 2 x 60 min/wk of resistance training (9 resistance training exercises including Cybex strength training equipment and free weights exercises)	Usual care
Rogers et al. 2009	41 (21/20)	52	I-III	Aerobic	12 wks	Intervention consisting of 6 discussion group sessions; 12 individual supervised exercise sessions; 3 individual ‘‘face-to-face’’ update counselling sessions Behaviour change intervention with goal of gradually increasing all participants to 150 min/wk of moderate walking.	Wait list control
Saarto et al. 2011	77 (40/37)	52	I-III	Step aerobics and jump training	12 mo	1 x supervised and 2–3 x home-based unsupervised exercise for 50-60 min/wk at RPE 11–16 of step aerobics consisted 150 to 180 jumps and leaps and circuit-training consisted of 3 rounds of 8-10 different vigorous movements such as rope-jumping and skate-jumping resulting in a total of 100 to 150 jumps and leaps during each session. In addition, home-based circuit training and aerobic exercise.	Usual care
Schmitz et al. 2005	86 (43/43)	53	0-III	Resistance	6 mo	2 x 60 min/wk of 9 common weight-training exercises using variable resistance machines and free weights (for muscles of the chest, back, shoulders, and arms, buttocks, hips, and thighs). Starting at lightest weight; progressed 1 set to 3 sets of 8–10 repetitions	Wait list control
Schmitz et al. 2009	295 (148/147)	56	0-III	Resistance	12 mo	2 x 90 min/wk of resistance training consisting of upper and lower body exercises. Weight was increased for each exercise by the smallest possible increment after 2 sessions of completing 3 sets of 10 repetitions with no change in arm symptoms.	Wait list control

Study	Sample N (intervention /control)	Mean age /range (y)	Stage	Mode	Intervention duration	Intervention details	Control group details
Sprod et al. 2010	114 (97/29)	59	NR	Aerobic and resistance	3 and 6 mo	2-3 x 60 min/wk of aerobic exercise at 30 to 55% of heart rate reserve, and resistance training and flexibility exercises emphasizing all of the major muscle groups.	Usual care
Vallance et al. 2007	337 (285/96)	59	I-III	Aerobic	12 wks	5 x 30 min/wk of moderate/vigorous activity	Standard health guidelines
Winters-Stone et al. 2011	106 (52/54)	63	0-III	Resistance	12 mo	3 x 45-60 min/wk of resistance training at loads corresponding to 60–70% of 1-RM for 1–3 sets of 8–12 repetitions of upper and lower body exercises, and Impact exercise consisted of jumps from the ground to a target height 1″ from the floor, performed with weighted vests and in sets of 10. Participants performed 1–6 jump sets, 1–2 sets of 3–4 upper body, and 3–4 lower body exercises.	Flexibility (stretching exercise) control

Overall study characteristics

Of the 34 included trials, 31 were RCTs, one study (Heim et al., 2007) used a quasi-randomised design to allocate participants to treatment and two were controlled clinical trials (Hutnick et al., 2005; Sprod et al., 2010). All trials, except for four (DeNysschen et al., 2011; Daley et al., 2007; Sprod et al., 2010; Vallance et al., 2007), randomized eligible participants to either the exercise or comparison arm. The additional study group in three of the four trials comprised variations in the exercise intervention arm, such as six or three month exercise groups (Sprod et al., 2010), an exercise-related print material group or a pedometer group or a combination of print material and pedometer group (Vallance et al., 2007), and an exercise during and after treatment group or an exercise after treatment only group (DeNysschen et al., 2011). In all, 3,051 (mean=90; range=16-573) participants were randomized to an exercise intervention(s) (n of participants=1,720; mean=52; range=8-302) or the comparison group (n=1,319; mean=40; range=8-271).

Study participants

Twenty three trials reported cancer stage data (Cadmus et al., 2009; Cantarero-Villanueva et al., 2011; Carson et al., 2009; Cho et al., 2006; Courneya et al., 2003; DeNysschen et al., 2011; Fillion et al., 2008; Herrero et al., 2006; Hutnick et al., 2005; Ligibel et al., 2008; Littman et al., 2012; Matthews et al., 2007; Mefferd et al., 2007; Mehnert et al., 2011; Milne et al., 2008; Musanti, 2012; Pinto et al., 2003; Pinto et al., 2005; Rogers et al., 2009; Schmitz et al., 2005; Schmitz et al., 2009; Vallance et al., 2007; Winters-Stone et al., 2011). Of these 23, eight included participants with stage 0 breast cancer (n=73, range=1-28) (Cadmus et al.,

2009; Fillion et al., 2008; Littman et al., 2012; Pinto et al., 2003; Pinto et al., 2005; Schmitz et al., 2005; Schmitz et al., 2009; Winters-Stone et al., 2011), all 23 trials consisted of participants with both stage I and II breast cancer (n=784, range=7-194 and n=753, range=3-161, respectively), and 18 trials included stage III breast cancer patients (n=175, range=1-50) (Cadmus et al., 2009; Cantarero-Villanueva et al., 2011; Courneya et al., 2003; DeNysschen et al., 2011; Fillion et al., 2008; Hutnick et al., 2005; Littman et al., 2012; Ligibel et al., 2008; Matthews et al., 2007; Mefferd et al., 2007; Mehnert et al., 2011; Milne et al., 2008; Musanti, 2012; Rogers et al., 2009; Schmitz et al., 2005; Schmitz et al., 2009; Vallance et al., 2007; Winters-Stone et al., 2011). Six of the trials that included participants stage data reported missing stage data (n=38, range=2-15) (Herrero et al., 2006; Hutnick et al., 2005; Ligibel et al., 2008; Matthews et al., 2007; Schmitz et al., 2009; Winters-Stone et al., 2011).

Fourteen trials reported the participants' average time since cancer diagnosis, ranging from 3.5 to 62.5 months (Cadmus et al., 2009; Carson et al., 2009; Cho et al., 2006; Fillion et al., 2008; Ligibel et al., 2008; Littman et al., 2012; Matthews et al., 2007; Mefferd et al., 2007; Pinto et al., 2003; Pinto et al., 2005; Schmitz et al., 2005; Schmitz et al., 2009; Vallance et al., 2007; Winters-Stone et al., 2011). Twelve trials reported the average time beyond active treatment, which ranged from one week after the end of treatment to 41.8 months beyond the end of active cancer treatment (Courneya et al., 2003; Daley et al., 2007; Herrero et al., 2006; Hutnick et al., 2005; Milne et al., 2008; Mustian et al., 2004; Pinto et al., 2003; Rogers et al., 2009; Saarto et al., 2011; Schmitz et al., 2005; Sprod et al., 2010).

Twenty eight trials reported the number of participants who had received chemotherapy (Bower et al., 2011; Cadmus et al., 2009; Cantarero-Villanueva et al., 2011; Carson et al., 2009; Cho et al., 2006; Courneya et al., 2003; Daley et al., 2007; DeNysschen et al., 2011; Fillion et al., 2008; Heim et al., 2007; Herrero et al., 2006; Hutnick et al., 2005; Ligibel et al., 2008; Matthews et al., 2007; Milne et al., 2008; Musanti, 2012; Mustian et al., 2004; Nikander et al., 2007; Pinto et al., 2003; Pinto et al., 2005; Rahnama et al., 2010; Rogers et al., 2009; Saarto et al., 2011; Schmitz et al., 2005; Schmitz et al., 2009; Sprod et al., 2010; Vallance et al., 2007; Winters-Stone et al., 2011). The mean percentage of participants who had received chemotherapy was 68.3% (range=30-100%). Three trials consisted entirely of participants who had received chemotherapy (Herrero et al., 2006; Hutnick et al., 2005; Rahnama et al., 2010).

Twenty five of the 34 trials reported participant's hormone therapy details (Bower et al., 2011; Cadmus et al., 2009; Carson et al., 2009; Cho et al., 2006; Courneya et al., 2003; Daley et al., 2007; Fillion et al., 2008; Heim et al., 2007; Ligibel et al., 2008; Matthews et al., 2007; Mefferd et al., 2007; Milne et al., 2008; Musanti, 2012; Mustian et al., 2004; Nikander et al., 2007; Payne et al., 2008; Pinto et al., 2003; Pinto et al., 2005; Rahnama et al., 2010; Rogers et al., 2009; Saarto et al., 2011; Schmitz et al., 2005; Schmitz et al., 2009; Vallance et al., 2007; Winters-Stone et al., 2011). The total number of participants who received hormone therapy in these 25 trials was 1,600 (mean=64; range=16-442). Selective oestrogen receptor modulator (SORM) use was reported in 10 trials (Cadmus et al., 2009; Carson et al., 2009; Ligibel et al., 2008; Matthews et al., 2007; Mefferd et al., 2007; Rogers et al., 2009; Schmitz et al., 2005; Schmitz et

al., 2009; Vallance et al., 2007; Winters-Stone et al., 2011), while aromatase inhibitors (AI) use was reported in eight trials (Cadmus et al., 2009; Carson et al., 2009; Ligibel et al., 2008; Rogers et al., 2009; Schmitz et al., 2005; Schmitz et al., 2009; Vallance et al., 2007; Winters-Stone et al., 2011). A total of 469 participants (mean=47; range=11-182) had taken SORMs, and a total of 188 had taken AI (mean=24; range=2-43).

The mean age of participants in the 32 trials that reported this characteristic was 54.3 (mean age range=49-65) y, while two trials reported the age ranges of participants (Heim et al., 2007; Rahnama et al., 2010). Postmenopausal status was reported in 18 of the trials (Bower et al., 2011; Cadmus et al., 2009; Cantarero-Villanueva et al., 2011; Carson et al., 2009; Courneya et al., 2003; DeNysschen et al., 2011; Fillion et al., 2008; Ligibel et al., 2008; Matthews et al., 2007; Mefferd et al., 2007; Milne et al., 2008; Pinto et al., 2003; Payne et al., 2008; Rogers et al., 2009; Saarto et al., 2011; Schmitz et al., 2005; Vallance et al., 2007; Winters-Stone et al., 2011), and the mean percentage of postmenopausal participants in these trials was 72.2% (average range=0-100). Five of the trials had exclusively postmenopausal participants (Cadmus et al., 2009; Courneya et al., 2003; Matthews et al., 2007; Payne et al., 2008; Winters-Stone et al., 2011), while Bower et al. (2011) consisted of only pre- and peri-menopausal participants. One trial stated the number of participants who reported menopause symptoms rather than menopausal status (Heim et al., 2007).

The ethnicity of the participants was reported by 15 trials (Bower et al., 2011; Cadmus et al., 2009; Carson et al., 2009; Daley et al., 2007;

DeNysschen et al., 2011; Littman et al., 2012; Matthews et al., 2007; Mefferd et al., 2007; Musanti, 2012; Mustian et al., 2004; Payne et al., 2008; Pinto et al., 2005; Rogers et al., 2009; Schmitz et al., 2005; Schmitz et al., 2009). The majority of the participants were white (mean %=87.6%, range=64.5-98%), while black participants were the next highest ethnic group (n trials=11; mean %=10.3%, average range=1-31%).

Eighteen trials reported the education of the participants (Bower et al., 2011; Cadmus et al., 2009; Cantarero-Villanueva et al., 2011; Carson et al., 2009; Cho et al., 2006; Courneya et al., 2003; Daley et al., 2007; Fillion et al., 2008; Hutnick et al., 2005; Littman et al., 2011; Mehnert et al., 2011; Mustian et al., 2004; Payne et al., 2008; Pinto et al., 2003; Pinto et al., 2005; Schmitz et al., 2005; Schmitz et al., 2009; Vallance et al., 2007), with an average of 46% (range=22-70.3%) of participants reporting educational attainment of a university degree or more. Three additional trials reported number of years in education (mean=15y, mean range=14-16y) (Matthews et al., 2007; Rogers et al., 2009; Saarto et al., 2011).

Eleven trials reported on the socio-demographic status of the participants (Bower et al., 2011; Courneya et al., 2003; DeNysschen et al., 2011; Fillion et al., 2008; Littman et al., 2012; Mustian et al., 2004; Payne et al., 2008; Pinto et al., 2003; Pinto et al., 2005; Rogers et al., 2009; Vallance et al., 2007). Four trials reported the specific co-morbidities of participants (Cadmus et al., 2009; Daley et al., 2007; Saarto et al., 2011; Vallance et al., 2007), while an additional two trials reported a co-morbidity index score (Rogers et al., 2009; Winters-Stone et al., 2011), and one trial consisted of a study arm of participants with lymphedema (Schmitz et al.,

2009). Sixteen trials reported on the past physical activity history or baseline physical activity of the participants (Cadmus et al., 2009; Cantarero-Villanueva et al., 2011; Courneya et al., 2003; Daley et al., 2007; Fillion et al., 2008; Heim et al., 2007; Ligibel et al., 2008; Littman et al., 2012; Matthews et al., 2007; Mehnert et al., 2011; Musanti, 2012; Pinto et al., 2005; Saarto et al., 2011; Schmitz et al., 2009; Vallance et al., 2007; Winters-Stone et al., 2011).

Twenty one trials reported the mean body mass of participants (Cadmus et al., 2009; Courneya et al., 2003; Daley et al., 2007; DeNysschen et al., 2011; Heim et al., 2007; Herrero et al., 2006; Hutnick et al., 2005; Ligibel et al., 2008; Littman et al., 2012; Matthews et al., 2007; Mefferd et al., 2007; Musanti, 2012; Nieman et al., 1995; Nikander et al., 2007; Pinto et al., 2003; Rahnama et al., 2010; Saarto et al., 2011; Schmitz et al., 2009; Sprod et al., 2010; Vallance et al., 2007; Winters-Stone et al., 2011) and 21 trials reported participants mean BMI scores (Bower et al., 2011; Cadmus et al., 2009; Courneya et al., 2003; Daley et al., 2007; Herrero et al., 2006; Hutnick et al., 2005; Ligibel et al., 2008; Littman et al., 2012; Matthews et al., 2007; Mefferd et al., 2007; Milne et al., 2008; Mustian et al., 2004; Nikander et al., 2007; Pinto et al., 2003; Pinto et al., 2005; Rahnama et al., 2010; Rogers et al., 2009; Saarto et al., 2011; Schmitz et al., 2009; Vallance et al., 2007; Winters-Stone et al., 2011). The average mean body mass in these trials was 74.9 kg (range=67.2-84.7 kg), and the average mean BMI was 28.3 (range=24.6-30.9 $m \cdot kg^2$). One additional trial reported the number of participants that fell into particular BMI ranges (Heim et al., 2007).

Interventions

Intervention length ranged from four weeks (Fillion et al., 2008) to 12 months (Cadmus et al., 2009; Schmitz et al., 2009; Winters-Stone et al., 2011). The modal intervention length was 12 weeks (Bower et al., 2011; Courneya, et al., 2003; Matthews et al., 2007; Milne et al., 2008; Musanti, 2012; Mustian et al., 2004; Nikander et al., 2007; Pinto et al., 2003; Pinto et al., 2005; Rogers et al., 2009; Vallance et al., 2007). Eight trials had a follow-up period beyond the end of the intervention length (Bower et al., 2011; Cantarero-Villanueva et al., 2011; Carson et al., 2009; Daley et al., 2007; Fillion et al., 2008; Mefferd et al., 2007; Pinto et al., 2005; Rogers et al., 2009; Vallance et al., 2007). Follow-up duration ranged from two weeks to 12 months.

Mode of exercise differed across trials. Only three trials consisted of resistance training interventions with no form of aerobic exercise (i.e. any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature) included (Schmitz et al., 2005; Schmitz et al., 2009; Winters-Stone et al., 2011). Thirteen trials involved interventions that combined resistance training and aerobic exercise (Cantarero-Villanueva et al., 2011; Heim et al., 2007; Herrero et al., 2006; Hutnick et al., 2005; Kaltsatsou et al., 2011; Ligibel et al., 2008; Mefferd et al., 2007; Milne et al., 2008; Musanti, 2012; Niemen et al., 1995; Pinto et al., 2003; Rahnama et al., 2010; Sprod et al., 2010). Of these trials seven consisted of an intervention in which the resistance training and aerobic exercise was performed in the same training session (Herrero et al., 2006; Hutnick et al., 2005; Kaltsatsou et al., 2011; Milne et al., 2008; Niemen et al., 1995; Pinto et al., 2003; Sprod et al., 2010), while in three trials the

resistance training and aerobic exercise were performed on separate days (Heim et al., 2007; Ligibel et al., 2008; Rahnama et al., 2010) and in two trials this information was unclear (Cantarero-Villanueva et al., 2011; Mefferd et al., 2007). Interventions in 18 of the trials consisted of aerobic exercise only (Bower et al., 2011; Cadmus et al., 2009; Carson et al., 2009; Cho et al., 2006; Courneya et al., 2003; Daley et al., 2007; DeNysschen et al., 2011; Fillion et al., 2008; Littman et al., 2012; Matthews et al., 2007; Mehnert et al., 2011; Mustian et al., 2004; Nikander et al., 2007; Payne et al., 2008; Pinto et al., 2008; Rogers et al., 2009; Saarto et al., 2011; Vallance et al., 2007). One trial had separate aerobic exercise, resistance exercise and combined aerobic and resistance exercise intervention groups (Musanti, 2012).

The frequency of exercise ranged between two days to seven days per week and in some trials participants attended exercise sessions at a facility such as a gym, community centre, or university or hospital facility, while in others, participants were instructed to perform home-based exercise. Duration of exercise sessions ranged from 15 to more than 95 minutes, with a modal duration of 60 minutes (n=11; Cantarero-Villanueva et al., 2011; Fillion et al., 2008; Mefferd et al., 2007; Milne et al., 2008; Mustian et al., 2004; Niemen et al., 1995; Nikander et al., 2007; Saarto et al., 2011; Schmitz et al., 2005; Sprod et al., 2010; Winters-Stone et al., 2011). Two studies gave participants a goal total number of minutes of physical activity to achieve each week (range=90-150 min) (Rogers et al., 2009; Ligibel et al., 2008). In some trials the frequency of the exercise programme and duration of each exercise session increased during the

course of the trial. The total number of exercise sessions ranged between 12 and 260.

In 31 trials that consisted of aerobic exercise, eight consisted of walking only (Fillion et al., 2008; Heim et al., 2007; Matthews et al., 2007; Musanti, 2012; Niemen et al., 1995; Payne et al., 2008; Rahnama et al., 2010; Rogers et al., 2009), two involved primarily walking (Cadmus et al., 2009; Vallance et al., 2007), one trial involved treadmill or outdoor walking or running only (Hutnick et al., 2005) and one consisted of walking with gymnastics (Mehnert et al., 2011). Other aerobic intervention modes involved cycling only (Courneya et al., 2003; Herrero et al., 2006), “fast working arm movements” (Cantarero-Villanueva et al., 2011), step aerobics and circuit training (Nikander et al., 2007; Saarto et al., 2011), Greek dance (Kaltsatsou et al., 2011), Tai Chi Chaung (Mustian et al., 2004) and Yoga (Bower et al., 2011; Carson et al., 2009; Littman et al., 2012). In all other trials participants chose their preferred option from a range of modes (Daley et al., 2007; DeNysschen et al., 2011; Mefferd et al., 2007; Milne et al., 2008; Pinto et al., 2003; Pinto et al., 2005; Sprod et al., 2010).

The frequency of aerobic exercise ranged from one to seven days per week. The frequency of aerobic exercise was between three and five days for 20 of the trials (Cadmus et al., 2009; Cantarero-Villanueva et al., 2011; Courneya et al., 2003; Daley et al., 2007; DeNysschen et al., 2011; Fillion et al., 2008; Herrero et al., 2006; Hutnick et al., 2005; Kaltsatsou et al., 2011; Littman et al., 2012; Matthews et al., 2007; Milne et al., 2008; Musanti, 2012; Mustian et al., 2004; Nikander et al., 2007; Niemen et al.,

1995; Pinto et al., 2003; Payne et al., 2008; Saarto et al., 2011; Vallance et al., 2007). Duration of aerobic exercise ranged between 10 to 90 minutes. Nine trials included aerobic exercise sessions with durations that either progressed to or was set at 30 minutes throughout (Cadmus et al., 2009; Courneya et al., 2003; DeNysschen et al., 2011; Heim et al., 2007; Herrero et al., 2006; Musanti, 2012; Pinto et al., 2003; Pinto et al., 2005; Rahnama et al., 2010; Vallance et al., 2007).

The intensity of the aerobic exercise varied substantially between trials as did the methods used to measure and monitor intensity. Three of the trials did not provide the intensity at which the aerobic exercise was performed (Cantarero-Villanueva et al., 2011; Fillion et al., 2008; Heim et al., 2007). Twelve trials set intensity based upon percentage of maximum heart rate (MHR range: 40% to 80%) (Cadmus et al., 2009; Cho et al., 2006; Daley et al., 2007; Herrero et al., 2006; Kaltsatsou et al., 2011; Ligibel et al., 2008; Milne et al., 2008; Musanti, 2012; Niemen et al., 1995; Pinto et al., 2003; Pinto et al., 2005; Rahnama et al., 2010), one used percentage of heart rate reserve (HRR range: 30 to 55%) (Sprod et al., 2010), three studies used percentage of directly measured maximal oxygen uptake (VO_2 max range: 60 to 75%) (Courneya et al., 2003; Hutnick et al., 2005; Mehnert et al., 2011), five studies utilised rate of perceived exertion (RPE range: 11-16) (Daley et al., 2007; DeNysschen et al., 2011; Matthews et al., 2007; Nikander et al., 2007; Saarto et al., 2011), and five trials measured intensity subjectively (either moderate or moderate to vigorous intensity) (Mefferd et al., 2007; Mustian et al., 2004; Payne et al., 2008; Rogers et al., 2009; Vallance et al., 2007).

The frequency of resistance training interventions ranged between two and three days, with a modal frequency of three days (n=8; Cantarero-Villanueva et al., 2011; Kaltsatsou et al., 2011; Heim et al., 2007; Herrero et al., 2006; Hutnick et al., 2005; Milne et al., 2008; Musanti, 2012; Niemen et al., 1995; Pinto et al., 2003; Winters-Stone et al., 2011). Two trials started with two days and progressed to three days (Mefferd et al., 2007; Sprod et al., 2010). Duration of resistance training sessions ranged between 25 and 90 minutes. The number of resistance exercises ranged between four and 12, with a modal exercise number of nine (n=4; Heim et al., 2007; Rahnama et al., 2010; Schmitz et al., 2005; Schmitz et al., 2009). Nine trials consisted of resistance training exercises for both the upper and lower body (Cantarero-Villanueva et al., 2011; Herrero et al., 2006; Hutnick et al., 2005; Milne et al., 2008; Musanti, 2012; Rahnama et al., 2010; Schmitz et al., 2005; Schmitz et al., 2009; Winters-Stone et al., 2011), one targeted the lower body and abdominals (Ligibel et al., 2008), one targeted the upper body and abdominals (Pinto et al., 2003) and one targeted the upper body only (Kaltsatsou et al., 2011), while the remaining studies did not report the areas of the body that the exercises targeted (Heim et al., 2007; Mefferd et al., 2007; Niemen et al., 1995; Sprod et al., 2010). One study combined resistance training with jump exercises with added resistance ranging from 0% to 10% of bodyweight (Winters-Stone et al., 2011).

Eight trials reported the equipment that was utilized in the resistance training sessions. Resistance machines were used in five trials (Kaltsatsou et al., 2011; Ligibel et al., 2008; Rahnama et al., 2010; Schmitz et al., 2005; Schmitz et al., 2009), free weights (i.e. dumbbells and barbells)

were utilised in five trials (Rahnama et al., 2010; Schmitz et al., 2005; Schmitz et al., 2009; Pinto et al., 2003; Winters-Stone et al., 2011), and resistance bands was used in four trials (Cantarero-Villanueva et al., 2011; Hutnick et al., 2005; Musanti, 2012; Winters-Stone et al., 2011). The number of sets per resistance exercise ranged from one to four, and the number of repetitions per set ranged between eight and 15. The intensity of resistance exercises was set according to the percentage of maximum weight a participant can lift for a set number of repetitions in four trials (Cantarero-Villanueva et al., 2011; Herrero et al., 2006; Ligibel et al., 2008; Winters-Stone et al., 2011) and RPE in one trial (Musanti, 2012).

In six of the trials, participants in the intervention group took part in psychosocial or behavioural counselling sessions or discussion groups (Carson et al., 2009; Cho et al., 2006; Fillion et al., 2008; Matthews et al., 2007; Mefferd et al., 2007; Rogers et al., 2009). The number of counselling sessions ranged from one to 16 in the five trials that reported this information (Carson et al., 2009; Cho et al., 2006; Fillion et al., 2008; Matthews et al., 2007; Rogers et al., 2009), and the duration of these sessions was 30 to 90 minutes in the four trials which reported session duration (Carson et al., 2009; Cho et al., 2006; Fillion et al., 2008; Matthews et al., 2007). Two trials claimed to integrate cognitive behavioural therapy techniques or behavioural coping strategies during exercise sessions (Daley et al., 2008; Mustian et al., 2004), one trial incorporated individual meetings designed to outline goals and provide feedback on participants progress (Courneya et al., 2003), one trial mailed physical activity tips to participants in the intervention (Pinto et al., 2005), while in another trial both intervention and control groups received an

educational programme, physical therapy, group exercise and psycho-oncological interventions (Heim et al., 2007). In three of the trials incorporating psychosocial or behavioural counselling sessions into the intervention, these sessions were complimented with telephone counselling during the intervention period (Fillion et al., 2008; Matthews et al., 2007; Mefferd et al., 2007). The number of telephone counselling sessions ranged between four and 18, and their duration ranged from five to 15 minutes. Five additional trials involved telephone calls in order to track and review the progress of participants in the intervention groups (Courneya et al., 2003; DeNysschen et al., 2011; Hutnick et al., 2005; Musanti, 2012; Pinto et al., 2005).

Interventions in 27 trials involved a supervised component, while 19 trials involved a home-based exercise component. In terms of the format of implementing the exercise programme, each used a group or individual format and an additional ten trials used a combined group and individual format (Bower et al., 2011; Cantarero-Villanueva et al., 2011; Carson et al., 2009; Cho et al., 2006; Courneya et al., 2003; Littman et al., 2012; Mefferd et al., 2007; Nikander et al., 2007; Rogers et al., 2009; Winters-Stone et al., 2011). The majority of trials (n=25; Bower et al., 2011; Cadmus et al., 2009; Cantarero-Villanueva et al., 2011; Carson et al., 2009; Cho et al., 2006; Courneya et al., 2003; Daley et al., 2007; Kaltsatsou et al., 2011; Fillion et al., 2008; Herrero et al., 2006; Hutnick et al., 2005; Ligibel et al., 2008; Littman et al., 2012; Mefferd et al., 2007; Mehnert et al., 2011; Milne et al., 2008; Mustian et al., 2004; Niemen et al., 1995; Pinto et al., 2003; Rahnama et al., 2010; Saarto et al., 2011; Schmitz et al., 2005; Schmitz et al., 2009; Sprod et al., 2010; Winters-

Stone et al., 2011) implemented the exercise programme in a facility such as a gym/sports club, community centre, or university or hospital facility. Fourteen trials involved a combination of facility and home-based exercise (Cadmus et al., 2009; Carson et al., 2009; Cho et al., 2006; Cantarero-Villanueva et al., 2011; Fillion et al., 2008; Heim et al., 2007; Hutnick et al., 2005; Ligibel et al., 2008; Littman et al., 2012; Mefferd et al., 2007; Nikander et al., 2007; Rogers et al., 2009; Saarto et al., 2011; Winters-Stone et al., 2011), while six trials were solely home-based (DeNysschen et al., 2011; Heim et al., 2007; Mathews et al., 2007; Musanti, 2012; Payne et al., 2008; Pinto et al., 2005; Vallance et al., 2007). The majority of the trials (n=25; Bower et al., 2011; Cadmus et al., 2009; Cantarero-Villanueva et al., 2011; Carson et al., 2009; Cho et al., 2006; Courneya et al., 2003; Daley et al., 2007; DeNysschen et al., 2011; Kaltsatsou et al., 2011; Fillion et al., 2008; Heim et al., 2007; Herrero et al., 2006; Hutnick et al., 2005; Ligibel et al., 2008; Littman et al., 2012; Matthews et al., 2007; Mehnert et al., 2011; Milne et al., 2008; Mustian et al., 2004; Rogers et al., 2009; Saarto et al., 2011; Schmitz et al., 2005; Schmitz et al., 2009; Sprod et al., 2010; Winters-Stone et al., 2011) enlisted the services of exercise physiologists, exercise/sports trainers/specialists, fitness/exercise instructors, physical and sports therapists, kinesiologists, yoga instructors or other professionals to lead the exercise programme.

In the majority of trials (n=25) the comparison arm was described as “usual” or “standard” care, “no intervention” or “sedentary control” and for 14 of these trials the comparison arm was a ‘waiting list’ control wherein participants were offered either a portion or the full exercise programme at the completion of the trial (Cadmus et al., 2009; Carson et al., 2009; Cho

et al., 2006; Courneya et al., 2003; Ligibel et al., 2008; Littman et al., 2012; Matthews et al., 2007; Mefferd et al., 2007; Milne et al., 2008; Pinto et al., 2003; Pinto et al., 2005; Rogers et al., 2009; Schmitz et al., 2005; Schmitz et al., 2009). The comparison group in eight trials received an intervention that included health education (Bower et al., 2011), phone calls (DeNysschen et al., 2011), educational programme, physical therapy, group discussion exercises and psycho-oncological interventions (Heim et al., 2007), psychosocial support therapy (Mustian et al., 2004), light-intensity body conditioning/stretching (e.g. flexibility and passive stretching) exercises (Daley et al., 2007; Musanti, 2012; Winters-Stone et al., 2011) and an attention control (Milne et al., 2008; Pinto et al., 2005).

Outcome measures

Physical activity outcomes:

Physical activity was assessed using either self-report or objectively by pedometers or accelerometers. Self-report questionnaires used included the Leisure Score Index (LSI) of Godin leisure time exercise questionnaire (Courneya et al., 2003; Musanti, 2012; Rogers et al., 2009; Vallance et al., 2007), the Community Health Activities Model Programme for Seniors (CAMPS) questionnaire (Mathews et al., 2007; Winters-Stone et al., 2011), the Minnesota Leisure Time Physical Activity Questionnaire (MLTPAQ) (Cantarero-Villanueva et al., 2011), a 7-day Physical Activity Log (PAL) (Cadmus et al., 2009), a 7-day physical Activity Recall (7-day PAR) (Mefferd et al., 2007; Pinto et al., 2005), the Baecke physical activity questionnaire (Schmitz et al., 2005), the International Physical Activity Questionnaire (IPAQ) (Schmitz et al., 2009), the Modifiable Activity Questionnaire (Littman et al., 2012) and self-developed physical activity

measures (e.g. exercise logs) were used in four trials (Daley et al., 2007; Heim et al., 2007; Hutnick et al., 2005; Saarto et al., 2011). Three trials used pedometers to objectively measure physical activity (Cadmus et al., 2009; Nikander et al., 2007; Vallance et al., 2007), while another three used accelerometers (Matthews et al., 2007; Pinto et al., 2005; Rogers et al., 2009). Ten trials did not report participants' physical activity data (DeNysschen et al., 2011; Fillion et al., 2008; Herrero et al., 2006; Mehnert et al., 2011; Milne et al., 2008; Mustian et al., 2004; Niemen et al., 1995; Pinto et al., 2003; Rahnama et al., 2010; Sprod et al., 2010).

Cardiorespiratory fitness outcomes:

Cardiorespiratory fitness was assessed using maximal or submaximal tests for either direct or indirect measurement of VO_2 max/peak. Six trials directly measured VO_2 peak using a maximal exercise test (Courneya et al., 2003; DeNysschen et al., 2011; Fillion et al., 2008; Herrero et al., 2006; Hutnick et al., 2005; Mehnert et al., 2011), two trials used the Bruce protocol (Musanti, 2012; Sprod et al., 2010) and one trial used the modified Bruce protocol (Rahnama et al., 2010) to measure VO_2 max indirectly. Other cardiorespiratory assessments included 8-min single stage walking treadmill test (Daley et al., 2007), single stage walking treadmill test (Fillion et al., 2008), 6-min walking treadmill test (Kaltsatsou et al., 2011; Mustian et al., 2004; Nieman et al., 1995), 2-km walking test (Nikander et al., 2007; Saarto et al., 2011), Rockport 1-mile walk test (Pinto et al., 2005), Aerobic Power Index (API) cycle test (Milne et al., 2008), Naughton protocol (Rogers et al., 2009), 3-min step test (Mefferd et al., 2007) and Harvard step test (Heim et al., 2007). One trial used a peak graded exercise stress test on a cycle ergometer to assess exercise

tolerance (Pinto et al., 2003). Pulmonary function (forced vital capacity and forced expiratory volume in one second) was assessed in one trial (Sprod et al., 2010).

Anthropometric outcomes:

Anthropometric outcomes included body mass (Cadmus et al., 2009; Courneya et al., 2003; Daley et al., 2007; DeNysschen et al., 2011; Ligibel et al., 2008; Littman et al., 2012; Matthews et al., 2007; Mefferd et al., 2007; Musanti, 2012; Nikander et al., 2007; Rahnama et al., 2010; Rogers et al., 2009; Saarto et al., 2011; Schmitz et al., 2005; Schmitz et al., 2009; Winters-Stone et al., 2011), BMI (Cadmus et al., 2009; Courneya et al., 2003; Daley et al., 2007; Ligibel et al., 2008; Littman et al., 2012; Matthews et al., 2007; Nikander et al., 2007; Rahnama et al., 2010; Rogers et al., 2009; Schmitz et al., 2005; Schmitz et al., 2009), waist circumference (Cadmus et al., 2009; Ligibel et al., 2008; Littman et al., 2012; Musanti, 2012; Rahnama et al., 2010; Rogers et al., 2009; Schmitz et al., 2005), hip circumference (Cadmus et al., 2009; Ligibel et al., 2008; Littman et al., 2012; Rahnama et al., 2010; Rogers et al., 2009), and arm circumference (Musanti, 2012). Body composition was assessed using Dual Energy X-ray Absorptionometry (DEXA) (Cadmus et al., 2009; DeNysschen et al., 2011; Matthews et al., 2007; Mefferd et al., 2007; Rogers et al., 2009; Saarto et al., 2011; Schmitz et al., 2005; Schmitz et al., 2009; Winters-Stone et al., 2011), Bioelectrical Impedance Analysis (BIA) (Daley et al., 2007; Ligibel et al., 2008; Matthews et al., 2007; Musanti, 2012; Mustian et al., 2004), skinfold thickness (SKF) Courneya et al., 2003; Herrero et al., 2006), and multi-slice Magnetic Resonance

Imaging (MRI) (Herrero et al., 2006). One trial reported body fat percentage but did not provide the method used (Hutnick et al., 2005).

Muscular strength and endurance outcomes:

Thirteen trials measured muscular strength or muscular endurance as an outcome. Maximal isometric leg/back strength was assessed in three trials (Heim et al., 2007; Nikander et al., 2007; Rogers et al., 2009; Saarto et al., 2011), leg extension in one trial (Niemen et al., 1995), maximal grip strength was assessed in five trials (Kaltsatsou et al., 2011; Hutnick et al., 2005; Mustian et al., 2004; Rogers et al., 2009; Saarto et al., 2011) and maximal isometric arm flexor strength was measured in two trials (Heim et al., 2007; Nikander et al., 2007). Other muscular strength tests included "multifunction's test" (Heim et al., 2007), biceps and triceps curls (Hutnick et al., 2005), "maximal weight lifted for each exercise during strength training sessions" (Ligibel et al., 2008), "recording the weight used during the performance of specific exercises (i.e. bicep curls, leg presses and chest extensions)", six repetition maximum (6-RM) (Musanti, 2012) and 1-RM chest press and leg press (Schmitz et al., 2005; Schmitz et al., 2009).

Muscular endurance tests included trunk curl static endurance test (Cadmus et al., 2009), multiple sit-to-stand test (Cadmus et al., 2009; Herrero et al., 2006), maximal number of repetitions at 30-35% and 100-110% of bodyweight (Herrero et al., 2006), curl-up test (Musanti, 2012; Sprod et al., 2010), YMCA bench press endurance test (Musanti, 2012), and muscular endurance tests using leg press, bench press, lat pull-down and shoulder press machines and crunches with resistance dependent on body weight and age of participants and repetitions performed at a rate of

12.5 repetitions per minute until volitional fatigue (Sprod et al., 2010). Other physical fitness tests included a countermovement vertical jump (Nikander et al., 2007; Saarto et al., 2011), the figure-8 running agility test (Nikander et al., 2007; Saarto et al., 2011) and timed chair stands (Bower et al., 2011).

Cardiovascular function outcomes:

Resting systolic blood pressure was measured in three trials (Kaltsatsou et al., 2011; Rahnama et al., 2010; Musanti, 2012; Courneya 2003). Resting heart rate was reported in two of these studies (Kaltsatsou et al., 2011; Rahnama et al., 2010; Musanti, 2012) and HRR in one trial (Courneya et al., 2003).

HRQoL, fatigue and other psychosocial outcomes:

HRQoL assessment included a wide range of measures including the Functional Assessment of Cancer Therapy-General (FACT-G) (Cadmus et al., 2009; Courneya et al., 2003; Daley et al., 2007; Heim et al., 2007; Littman et al., 2012; Milne et al., 2008; Rogers et al., 2009), Functional Assessment of Cancer Therapy-Breast (FACT-B) (Cadmus et al., 2009; Courneya et al., 2003; Daley et al., 2007; Littman et al., 2012; Milne et al., 2008; Rogers et al., 2009; Vallance et al., 2007), European Organization for Research and Treatment of Cancer (EOTRC) Quality of Life Questionnaire-C30 (QLQ-C30) (Herrero et al., 2006; Mehnert et al., 2011; Saarto et al., 2011), Medical Outcomes Study Short Form-12 (MOS SF-12) (Fillion et al., 2008), MOS SF-36 (Cadmus et al., 2009; Mehnert et al., 2011; Schmitz et al., 2009), Cancer Rehabilitation Evaluation System

Short Form (CARES-SF) (Schmitz et al., 2005) and a 27-item developed by Chae-Choe (Cho et al., 2007).

Fatigue was measured using the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) (Courneya et al., 2003; Heim et al., 2007; Littman et al., 2012; Mustian et al., 2004; Rogers et al., 2009; Saarto et al., 2011; Vallance et al., 2007), Revised Piper Fatigue Scale (PFS) (Cantarero-Villanueva et al., 2011; Daley et al., 2007; Musanti et al., 2012; Payne et al., 2008; Sprod et al., 2010), Multidimensional Fatigue Inventory (MFI) (Bower et al., 2011; Fillion et al., 2008; Heim et al., 2007), Schwartz Cancer Fatigue Scale (SCFS) (Milne et al., 2008), fatigue subscale of Profile of Mood States (POMS) (Cantarero-Villanueva et al., 2011; Pinto et al., 2003), fatigue subscale of HIV Self-Efficacy Questionnaire adapted for breast cancer (Bower et al., 2011), linear analog scale for fatigue (Pinto et al., 2005) and on a 0 to 9 scale (Carson et al., 2009). Body image/self-esteem was measured using the Rosenberg Self-Esteem Scale (RSE) (Cadmus et al., 2009; Courneya et al., 2003; Musanti, 2012; Mustian et al., 2004), Body Esteem Scale (Pinto et al., 2003; Pinto et al., 2005), physical self-perception profile (Daley et al., 2007; Musanti, 2012), Body Image Questionnaire (BIQ) (Mehnert et al., 2011), Body Image and Relationships Scale (BIRS) (Schmitz et al., 2009) and Social Physique Anxiety Scale 7 (SPAS-7) (Milne et al., 2008).

Of the 13 trials that measured depression, three trials used the Centres for Epidemiological Studies Depression scale (CES-D) (Cadmus et al., 2009; Payne et al., 2008; Schmitz et al., 2005), five trials used the Beck Depression Inventory (BDI) (Bower et al., 2011; Daley et al., 2007;

Kaltsatsou et al., 2011; Saarto et al., 2011; Sprod et al., 2010), three trials used the Hospital Anxiety and Depression scale (HADS) (Heim et al., 2007; Mehnert et al., 2011; Musanti, 2012), and one trial used the depression subscale of POMS (Fillion et al., 2008; Pinto et al., 2003). Anxiety was measured using the HADS (Heim et al., 2007; Mehnert et al., 2011; Musanti, 2012), State-Trait Anxiety Scale (STAI) (Cadmus et al., 2009) and the anxiety subscale of POMS (Fillion et al., 2008; Pinto et al., 2003). Two trials assessed happiness (Cadmus et al., 2009; Courneya et al., 2003) and both of these trials used the Happiness Measure (HM).

Four trails (Bower et al., 2011; Carson et al., 2009; Payne et al., 2008; Rogers et al., 2009) assessed sleep quality and three of these four trials (Bower et al., 2011; Payne et al., 2008; Rogers et al., 2009) used the Pittsburgh Sleep Quality Index (PSI), while one used a sleep disturbance 0 to 9 scale (Carson et al., 2009). Other self-report HRQoL related outcomes included stress assessment using Cohen's 10-item perceived stress scale (Bower et al., 2011; Cadmus et al., 2009; Cantarero-Villanueva et al., 2011), Satisfaction with Life Scale (SWLS) (Daley et al., 2007), Life Satisfaction Inventory (LSI) (Kaltsatsou et al., 2011), Symptoms of Stress Inventory (SOSI) (Mehnert et al., 2011), Symptom Checklist-90 Revised (SCL-90R) (Mehnert et al., 2011), Symptom Checklist (DeNysschen et al., 2011), Karnofsky Performance Scale (KPS) (DeNysschen et al., 2011), Brief Pain Inventory (BPI) (Fillion et al., 2008), Social Barriers Scale (Mehnert et al., 2011), POMS (vigor-activity) (Fillion et al., 2008; Pinto et al., 2005), POMS total mood disturbance (Pinto et al., 2003; Pinto et al., 2005), emotional function using Positive and Negative Affect Scale (PANAS) (Pinto et al., 2003), basic psychological needs

satisfaction scale (BNS) (Milne et al., 2008), revised psychosocial adjustment questionnaire (Cho et al., 2007), Menopausal symptoms (Carson et al., 2009), Behavioral Regulation for Exercise Questionnaire 2 (BREQ-2), joint pain, stiffness, and physical function via 5-point Likert scale version (i.e., 1 = none to 5 = extreme) of 24-item Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Rogers et al., 2009) and perceived general health perspective measured based on a single question on health (Rogers et al., 2009).

Two trials (Schmitz et al., 2005; Schmitz et al., 2009) reported outcomes related to lymphedema. One trial (Schmitz et al., 2005) reported arm-circumference measurements, self-report of diagnosis and self-report of symptoms. While the other trial (Schmitz et al., 2009) assessed arm and hand swelling at one year, as measured through displaced water volume of the affected and unaffected limbs, incidence of exacerbations of lymphedema and number and severity of lymphedema symptoms (Schmitz et al., 2009).

Blood biomarker outcomes:

Insulin was assessed in five trials using a variety of different methods including an enzyme-linked immunosorbent assay (ELISA) kit (Cadmus et al., 2009), immunochemiluminometric assay (Ligibel et al., 2008; Rahnama et al., 2009; Schmitz et al., 2005), and radioimmunoassay (RIA) (Mustian et al., 2004). Glucose was determined by hexokinase ultraviolet assay (Ligibel et al., 2008; Rahnama et al., 2009), and colorometric reflectance spectrophotometry (Schmitz et al., 2005). Insulin resistance was assessed by the Homeostasis Model Assessment (HOMA) in three

trials (Ligibel et al., 2008; Rahnama et al., 2009; Schmitz et al., 2005). Total cholesterol (TC) was assessed in two trials (Courneya et al., 2003; Mefferd et al., 2007), high-density lipoprotein cholesterol (HDL-C) and triglycerides were measured in three trials (Courneya et al., 2003; Mefferd et al., 2007; Rahnama et al., 2009), low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula (Friedewald et al., 1972) in two trials (Courneya et al., 2003; Mefferd et al., 2007) and finally the TC:HDL-C ratio was calculated as total cholesterol divided by HDL-C in one trial (Courneya et al., 2003). All cholesterol outcomes were determined by assayed plasma using enzymatic methods. One trial determined haematocrit and haemoglobin levels using a Sysmex NE-1500 haematology analyzer (Herrero et al., 2006).

Additional blood biomarker outcomes included IGF-I (Cadmus et al., 2009: Mustian et al., 2004; Schmitz et al., 2005) determined via ELISA in two of these trials (Cadmus et al., 2009; Schmitz et al., 2005) and immunoradiometric assay in one (Mustian et al., 2004), and its binding proteins, IGFBP-1 by ELISA (Schmitz et al., 2005) and immunoradiometric assay (Mustian et al., 2004), IGFBP-2 by ELISA (Schmitz et al., 2005), and IGFBP-3 by ELISA (Cadmus et al., 2009; Schmitz et al., 2005) and immunoradiometric assay (Mustian et al., 2004). IGF-II was also measured in one trial via ELISA (Schmitz et al., 2005). Other blood biomarkers included leptin and adiponectin, assessed via radioimmunoassay and high molecular weight adiponectin (HMWA) by ELISA (Ligibel et al., 2008), cortisol by radioimmunoassay (Payne et al., 2008), and serotonin radioimmunoassay (Payne et al., 2008). One trial assessed salivary cortisol and IgA concentrations, and α-amylase activity

using a commercial luminescence immune assay (Cantarero-Villanueva et al., 2011).

Blood borne inflammatory biomarkers were assessed in five trials (Courneya et al., 2003; Hutnick et al., 2005; Mefferd et al., 2007; Mustian et al., 2004; Payne et al., 2008). Courneya (2003) assessed serum C-reactive protein (CRP) by ELISA, change in natural killer (NK) cell cytotoxic activity in isolated peripheral blood mononuclear cells, *w*hite blood cell counts and differential measured using a Coulter STKS instrument, whole blood neutrophil function quantified by flow cytometry, the phenotypes of isolated mononuclear cells by an immunofluorescence assay, estimations of unstimulated and phytohemagglutinin (PHA)-stimulated mononuclear cell function, rate of (^{3}H)-thymidine uptake, and the production of proinflammatory cytokines, interleukin (IL)-1α, Tumour Necrosis Factor-alpha (TNF-α) and IL-6 and anti-inflammatory cytokines IL-4, IL-10 and transforming growth factor-β1, by ELIZA. Hutnick et al. (2005) measured the numbers of $CD3^{+}$, $CD4^{+}$, $CD8^{+}$, B, and NK cells in fresh blood using immunochemistry and flow cytometry, lymphocyte proliferation determined by mitogen assays over a range of concentrations of the T-cell activators concanavalin A (ConA), phytohemagglutin (PHA) or pokeweed mitogen (PWM), and blood plasma concentration of IL-6, soluble IL-6 receptor (sIL-6R), soluble glycoprotein 130 (sgp130) and interferon-gamma (IFN-γ) as well as the activated lymphocyte supernatant concentration of IFN- γ and IL-6 were determined by ELISA. Mefferd et al. (2007) assessed levels of IL-6, TNF-α, IL-8 and Vascular Endothelial Growth Factor (VEGF) by ELISA. Mustian et al. (2004) assessed serum cytokines, IL-2, IL-6 and IFN-γ, by ELISA. Niemen et al. (1995) assessed

natural killer cell cytotoxic activity by chromium release assay and concentration of circulating immune cells, including percent total NK, total leukocytes, neutrophils, lymphocytes and T-cell subsets. Finally, Payne et al. (2008) determined IL-6 and bilirubin by radioimmunoassay.

Bone-related outcomes:

Bone mineral density (BMD) was assessed by DEXA in four trials (Cadmus et al., 2009; Rogers et al., 2009; Saarto et al., 2011; Winters-Stone et al., 2011). Bone turnover was assessed in one trial (Winters-Stone et al., 2011) by serum osteocalcin, a byproduct of bone formation and urinary deoxypyrodinoline cross-links (nmol/l), a byproduct of bone degradation adjusted for urine volume (creatinine: mmol/l), both determined by ELISA. Another trial assessed bone resorption using serum levels of *N*-telopeptides of type I collagen (NTx) determined by an enzyme-linked immunosorbent assay and a specific monoclonal antibody for NTx (osteomark serum NTx), and a marker of bone formation using serum levels of bone-specific alkaline phosphatase (BSAP), determined by a chemiluminescent immunoassay (Mustian et al., 2004). The authors of this trial (2004) investigated the balance between bone formation and bone resorption by using a formula developed by Eastell et al. 1993 to calculate a bone remodeling index (BRI). The formula is: Δ ZBSAP − Δ ZNTx, where ZBSAP = (BSAPObserved − BSAPμ at baseline)/σ at baseline, and ZNTx = (NTxObserved − NTxμ at baseline)/σ at baseline.

Joint range of motion outcomes:

Joint range of motion assessments were included in four trials (Cantarero-Villanueva et al., 2011; Cho et al., 2007; Musanti, 2012; Mustian et al.,

2004). Cantarero-Villanueva et al. (2011) measured shoulder flexion, extension, horizontal abduction and external rotation was assessed using a 41 cm plastic universal 2-arm goniometer and assessed cervical mobility using a cervical goniometric device. Musanti (2012) assessed hip flexion, hip backward extension, shoulder flexion, shoulder posterior elevation, and shoulder abduction using a goniometer. Finally, Mustian et al. (2004) measured shoulder flexion, extension, abduction, and adduction using goniometric measurements. Joint ROM outcomes were not included in the meta-analysis.

Excluded studies

The 96 trials retrieved and subsequently excluded did not meet the inclusion criteria for the following reasons. Trials were excluded if it was a single group trial or did not compare an exercise with a no exercise, exercise placebo (e.g. stretching), or usual care group (n=47), when breast cancer participants were not analysed separately (n=17), the trial included participants with metastatic disease (n=7), participants undergoing radiotherapy and/or chemotherapy (n=7) or participants who were pre-cancer therapy (n=1). Trials including interventions that did not promote or measure physical activity as an outcome (n=5), involved interventions that included therapeutic exercise regimes addressing only specific impairments related to the shoulder and arm or exercises restricted to stretching and/or local muscular endurance (n=7), or consisted of exercise combined with diet/medication where the effects of physical activity could not be isolated (n=2) were ineligible. Full details of excluded studies can be found in appendix G.

2.8.4.2 Risk of bias in included studies

The included studies were assessed for risk of bias using the “risk of bias” assessment tool and recommendations for judging risk of bias provided in Chapter eight of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2011). For each trial the risk of bias was detailed in the “risk of bias” tables included with the Characteristics of included studies and the “risk of bias” summary (Figure 2.8.2). In addition, an overall assessment of risk of bias is presented in Figure 2.8.3.

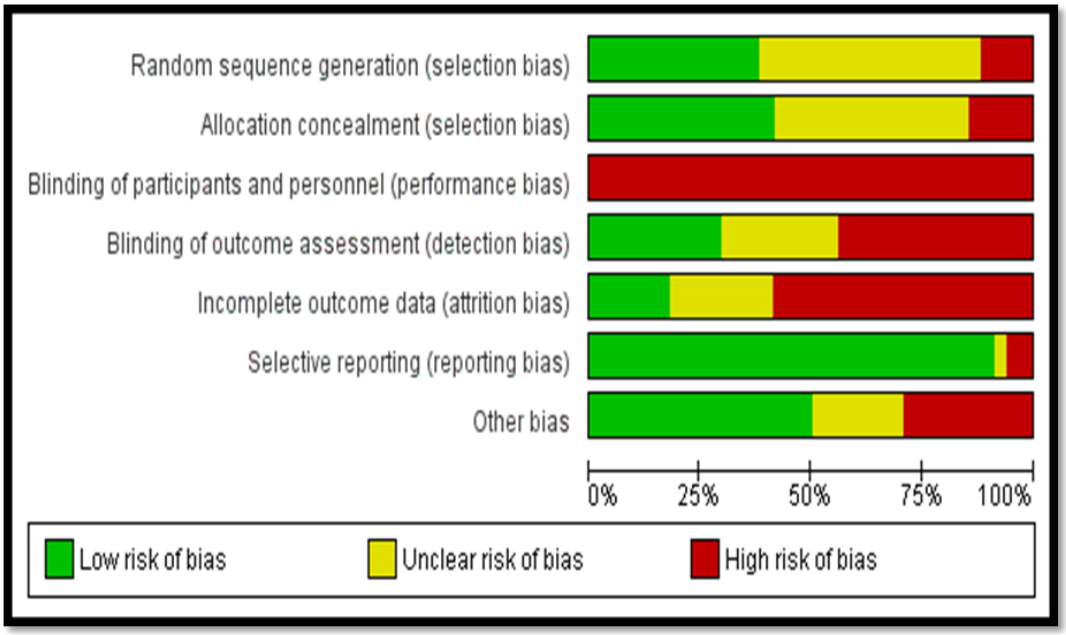


Figure 2.8.2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

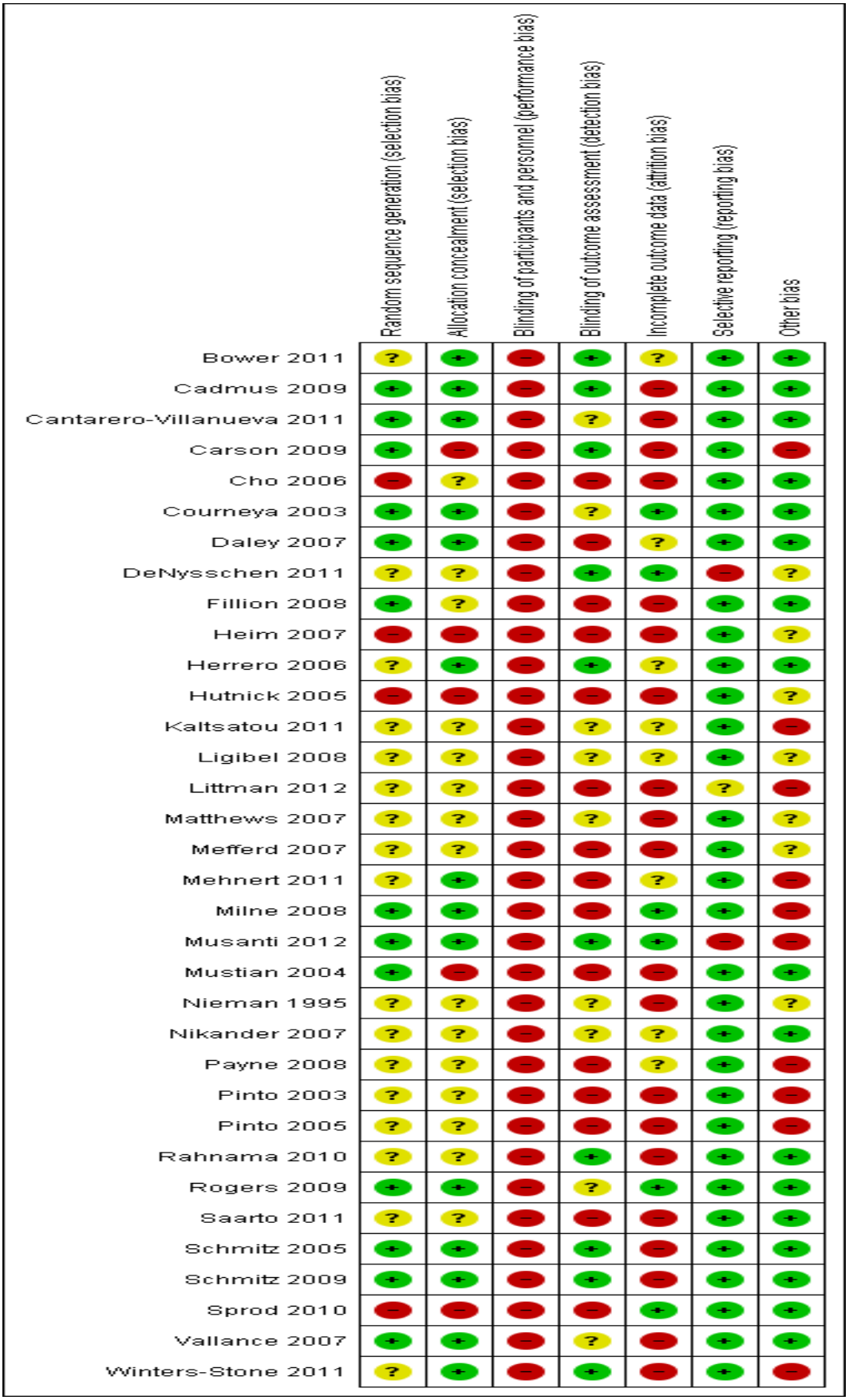


Figure 2.8.3 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Thirteen trials were at a low risk of selection bias due to adequate generation of the randomized sequence as the trials used a random component to generate their sequence (Cadmus et al., 2009; Cantarero-Villanueva et al., 2011; Carson et al., 2009; Courneya et al., 2003; Daley et al., 2007; Fillion et al., 2008; Milne et al., 2008; Musanti, 2012; Mustian et al., 2004; Rogers et al., 2009; Schmitz et al., 2005; Schmitz et al., 2009; Vallance et al., 2007). Four trials had a high risk of selection bias as they used a non-random component to generate their sequence (Cho et al., 2006; Heim et al., 2007; Hutnick et al., 2005; Sprod et al., 2010). Seventeen trials were considered to have an unclear risk of selection bias, mainly because the generation of the random sequence was not described (Bower et al., 2011; DeNysschen et al., 2011; Herrero et al., 2006; Kaltsatsou et al., 2011; Ligibel et al., 2008; Littman et al., 2012; Matthews et al., 2007; Mefferd et al., 2007; Mehnert et al., 2011; Nikander et al., 2007; Niemen et al., 1995; Payne et al., 2008; Pinto et al., 2003; Pinto et al., 2005; Rahnama et al., 2010; Saarto et al., 2011; Winters-Stone et al., 2011).

Fourteen trials were at a low risk of selection bias due to inadequate concealment of allocation to the intervention as the participants and investigators could not foresee assignment to the study groups (Bower et al., 2011; Cadmus et al., 2009; Cantarero-Villanueva et al., 2011; Courneya et al., 2003; Daley et al., 2007; Herrero et al., 2006; Milne et al., 2008; Mehnert et al., 2011; Musanti, 2012; Rogers et al., 2009; Schmitz et al., 2005; Schmitz et al., 2009; Vallance et al., 2007; Winters-Stone et al., 2011). Five trials were at a high risk of selection bias because there was a

possibility that participants and/or investigators could foresee assignment to the study groups (Carson et al., 2009; Heim et al., 2007; Hutnick et al., 2005; Mustian et al., 2004; Sprod et al., 2010). Fifteen trials were adjudged to have an unclear risk of selection bias due to allocation concealment, predominantly, because the allocation concealment was not described or not described in adequate detail for a decision to be made (Cho et al., 2006; DeNysschen et al., 2011; Fillion et al., 2008; Kaltsatsou et al., 2011; Ligibel et al., 2008; Littman et al., 2012; Matthews et al., 2007; Mefferd et al., 2007; Nikander et al., 2007; Nieman et al., 1995; Payne et al., 2008; Pinto et al., 2003; Pinto et al., 2005; Rahnama et al., 2010; Saarto et al., 2011).

Blinding

All trials included in this review were at high risk for performance bias because, owing to the nature of the intervention (i.e. physical activity), it was not possible to blind the trial personnel and participants. Ten trials were considered to be at a low risk of detection bias, because the outcome assessors were blinded to the allocation of participants to the study groups (Bower et al., 2011; Cadmus et al., 2009; Carson et al., 2009; DeNysschen et al., 2011; Herrero et al., 2006; Musanti, 2012; Rahnama et al., 2010; Schmitz et al., 2005; Schmitz et al., 2009; Winters-Stone et al., 2011), however, this was typically for outcome assessors measuring physical fitness and haematological outcomes rather than for self-report outcomes, such as HRQoL and psychological outcomes. Fifteen trials were at high risk for detection bias (Cho et al., 2006; Daley et al., 2007; Fillion et al., 2008; Heim et al., 2007; Hutnick et al., 2005; Littman et al., 2012; Mefferd et al., 2007; Mehnert et al., 2011; Milne et al.,

2008; Mustian et al., 2004; Payne et al., 2008; Pinto et al., 2003; Pinto et al., 2005; Saarto et al., 2011; Sprod et al., 2010). Nine trials had an unclear risk of detection bias (Cantarero-Villanueva et al., 2011; Courneya et al., 2003; Kaltsatsou et al., 2011; Ligibel et al., 2008; Matthews et al., 2007; Nikander et al., 2007; Niemen et al., 1995; Saarto et al., 2011; Vallance et al., 2007).

Incomplete outcome data

Six trials were at a low risk of attrition bias due to the amount, nature, or handling of incomplete outcome data. The decision of a high risk of attrition bias was based on the exclusion of participants with missing data, a lack of description of how missing data was handled or due to inappropriate methods of handling missing data, such as use of the last-observation-carried-forward (LOCF). Twenty trials had a high risk of attrition bias (Cadmus et al., 2009; Cantarero-Villanueva et al., 2011; Carson et al., 2009; Cho et al., 2006; Fillion et al., 2008; Heim et al., 2007; Hutnick et al., 2005; Littman et al., 2012; Matthews et al., 2007; Mefferd et al., 2007; Mustian et al., 2004; Niemen et al., 1995; Pinto et al., 2003; Pinto et al., 2005; Rahnama et al., 2010; Saarto et al., 2011; Schmitz et al., 2005; Schmitz et al., 2009; Vallance et al., 2007; Winters-Stone et al., 2011). Six trials were considered to be at a low risk of attrition bias either because the trials had no missing data or used an acceptable method for handling missing data (e.g. multiple imputation) (DeNysschen et al., 2011; Courneya et al., 2003; Milne et al., 2008; Musanti, 2012; Rogers et al., 2009; Sprod et al., 2010). Eight trials had an unclear risk of bias (Bower et al., 2011; Daley et al., 2007; Herrero et al., 2006; Kaltsatsou et al., 2011;

Ligibel et al., 2008; Mehnert et al., 2011; Nikander et al., 2007; Payne et al., 2008).

Selective reporting

Of the 34 trials, 31 were at a low risk of reporting bias, and based on the information provided by the trial authors, there was no reason to believe that there was selective reporting of the primary and secondary outcomes. Due to the incomplete reporting of outcome variables two trials (DeNysschen et al., 2011; Musanti, 2012) were considered at high risk for reporting bias, while one trial had an unclear risk (Littman et al., 2012).

Other potential sources of bias

Seventeen trials were at a low risk for other biases. Ten trials were considered to be at high risk for other biases (Carson et al., 2009; Kaltsatsou et al., 2011; Littman et al., 2012; Mehnert et al., 2011; Milne et al., 2008; Musanti, 2012; Payne et al., 2008; Pinto et al., 2003; Pinto et al., 2005; Winters-Stone et al., 2011) and seven trials were at unclear risk for other biases (DeNysschen et al., 2011; Heim et al., 2007; Hutnick et al., 2005; Ligibel et al., 2008; Matthews et al., 2007; Mefferd et al., 2007; Niemen et al., 1995) due to issues surrounding sample size, description of study sample and generalizability of findings**.**

For detailed information on outcomes, number of trials reporting the outcomes, number of participants on whom the outcomes were reported, statistical methods used for analysis, and effect estimates see the summary of findings table (table 2.8.2). The summary of findings from the subgroup analysis by intervention mode is presented in tables 2.8.3, 2.8.4

and 2.8.5. We based the meta-analysis on post-intervention values rather than change in score from baseline. Although using the change scores can remove a component of between-person variability from the analysis, it involves measurement of the outcome twice, which may make it less efficient for outcomes which are unstable or difficult to measure precisely (Deeks et al., 2008). We only included outcome assessments made immediately upon intervention completion rather than follow-up assessments made weeks or months after the post-intervention assessments. When heterogeneity was found, subgroups were investigated by intervention mode (aerobic, resistance training, combination of both, yoga or tai chi), method of measurement and presence of a psychological component. Sensitivity analysis of studies where the allocation concealment scored as low risk of bias versus unclear or with a high risk of bias was also conducted. Data was combined using a weighted MD when trials measured outcomes using either the same measurement method or scale to generate continuous data. We used an SMD analysis to combine data from different measurement methods measuring the same outcome.

For the meta-analysis, three of the intervention groups of Vallance et al. (2007) and the 3-month and 6-month intervention groups of Sprod and colleagues (2010) were combined using the methods outlined in chapter seven of the Cochrane handbook (Higgins and Deeks, 2010). Musanti (2012) consisted of aerobic exercise only, resistance training only and aerobic and resistance exercise combined intervention groups and a control group, therefore, for the combined physical activity analysis, the three intervention groups were combined, while when modes were

analysed separately the relevant interventions data were included. Schmitz et al. (2009) was separated into two studies, one study randomised breast cancer survivors with lymphedema into intervention and control groups, while the other separated breast cancer survivors at risk of lymphedema into intervention and control groups. Both studies were entered into the meta-analysis separately as Schmitz et al. (2009) (1) (with lymphedema) and Schmitz et al. (2009) (2) (at risk of lymphedema). Only data from a subgroup of 77 participants could be extracted from another study (Saarto et al., 2011), therefore, the data from this subgroup was included in the analysis.

2.8.4.3 Effects of interventions

Table 2.8.2 Summary of findings; analysis 1: all physical activity interventions vs. control

Outcome	Trial N	Sample N	Statistical Method	Effect Estimate (95% CI)	p-value/I^2
1.1 Physical activity levels (questionnaire data)	10	982	SMD (IV, Random, 95% CI)	0.57 (0.26, 0.89)	0.0004/79%
1.2 Physical activity (steps/day/week)	4	518	SMD(IV, Random, 95% CI)	0.29 (-0.20, 0.77)	0.25/75%
1.3 Cardiorespiratory fitness	16	734	SMD (IV, Random, 95% CI)	0.30 (0.05, 0.55)	0.02/61%
1.4 Mass (kg)	18	1103	MD (IV, Fixed, 95% CI (kg))	-1.61 (-3.38, 0.16)	0.07/0%
1.5. BMI (kg/m^2)	14	916	MD (IV, Fixed, 95% CI (kg/m^2))	-0.86 (-1.59, -0.13)	0.02/0%
1.6 Body Fat %	16	1025	SMD (IV, Fixed, 95% CI (%))	-0.15 (-0.28, -0.03)	0.02/9%
1.7. Lean mass (kg)	9	662	MD (IV, Fixed, 95% CI)	0.26 (-0.69, 1.21)	0.59/0%
1.8 Waist circumference (cm)	6	380	MD (IV, Fixed, 95% CI (cm))	-0.16 (-2.67, 2.35)	0.90/0%
1.9 Hip circumference (cm)	5	325	MD (IV, Random, 95% CI (cm))	0.56 (-5.30, 6.43)	0.85/82%
1.10 Waist-to-hip ratio (cm)	3	196	MD (IV, Fixed, 95% CI (cm))	-0.01 (-0.03, 0.02)	0.49/0%
1.11 Upper body strength	12	667	SMD (IV, Random, 95% CI)	0.61 (0.27, 0.94)	0.0004/76%
1.12 Lower body strength	8	549	SMD (IV, Random, 95% CI)	0.46 (0.12, 0.80)	0.008/72%
1.13 Resting systolic blood pressure (mm/Hg)	3	108	MD (IV, Fixed, 95% CI)	-4.69 (-7.45, -1.93)	0.0009/0%
1.14 HRQoL – General	11	657	SMD (IV, Random, 95% CI)	0.54 (0.22, 0.86)	0.0009/72%
1.15 HRQoL – FACT-G	5	354	MD (IV, Random, 95% CI)	7.94 (-0.51, 16.39)	0.07/90%
1.16 HRQoL – FACT-B	5	590	MD (IV, Random, 95% CI)	8.06 (-3.62, 19.75)	0.18/93%

Outcome	Trial N	Sample N	Statistical Method	Effect Estimate (95% CI)	p-value/I^2
1.17 Physical well-being	15	989	SMD (IV, Fixed, 95% CI)	0.35 (0.22, 0.47)	<0.001/72%
1.18 Mental/emotional well-being	15	978	SMD (IV, Fixed, 95% CI)	0.16 (0.03, 0.29)	0.01/51%
1.19 Fatigue	16	1261	SMD (IV, Random, 95% CI)	-0.33 (-0.59, -0.07)	0.01/76%
1.20 Self-esteem	8	441	SMD (IV, Random, 95% CI)	0.29 (0.01, 0.57)	0.04/50%
1.21 Depression	8	454	SMD (IV, Fixed, 95% CI)	-0.41 (-0.61, -0.21)	<0.001/4%
1.22 Anxiety	5	275	SMD (IV, Random, 95% CI)	-0.64 (-1.03, -0.26)	0.001/57%
1.23 Sleep	3	126	SMD (IV, Random, 95% CI)	-0.06 (-0.56, 0.44)	0.82/49%
1.24 Plasma Insulin	6	328	SMD (IV, Random, 95% CI)	-0.46 (-1.12, 0.21)	0.18/88%
1.25 Blood glucose	4	240	SMD (IV, Random, 95% CI)	-0.11 (-0.44, 0.22)	0.52/37%
1.26 HOMA	3	186	SMD (IV, Fixed, 95% CI)	-0.05 (-0.34, 0.24)	0.74/0%
1.27 High-density lipoprotein	3	158	SMD (IV, Random, 95% CI)	0.18 (-0.26, 0.62)	0.42/45%
1.28 Triglyceride	3	158	SMD (IV, Random, 95% CI)	-0.17 (-0.80, 0.45)	0.59/72%
1.29 Insulin-like Growth factor-1	4	219	SMD (IV, Random, 95% CI)	-0.20 (-0.54, 0.14)	0.25/33%
1.30 Insulin-like Growth Factor-Binding Protein 3	3	165	SMD (IV, Random, 95% CI)	-2.06 (-3.99, -0.12)	0.04/95%
1.31 Interleukin-6	4	132	SMD (IV, Fixed, 95% CI)	-0.05 (-0.41, 0.30)	0.76/0%
1.32 Interferon-gamma	3	62	SMD (IV, Random, 95% CI)	-1.35 (-2.71, 0.02)	0.05/79%

Table 2.8.3 Summary of findings; analysis 2: aerobic exercise only interventions vs. control

Outcome	Trial N	Sample N	Statistical Method	Effect Estimate (95% CI)	p-value/I^2
2.1 Physical activity levels (questionnaire data)	5	600	SMD (IV, Random, 95% CI)	0.55 (0.21, 0.88)	0.001/61%
2.2 Cardiorespiratory fitness	9	446	SMD (IV, Fixed, 95% CI)	0.30 (0.11, 0.49)	0.002/20%
2.3 Mass (kg)	7	380	MD (IV, Fixed, 95% CI (kg))	-1.62 (-4.80, 1.57)	0.32/0%
2.4 BMI (kg/m^2)	5	267	MD (IV, Fixed, 95% CI (kg/m^2))	-0.52 (-2.00, 0.95)	0.49/0%
2.5 Percentage Body Fat	7	379	SMD (IV, Fixed, 95% CI)	-0.08 (-0.28, 0.12)	0.45/0%
2.6 Lean mass (kg)	3	169	MD (IV, Fixed, 95% CI (kg))	0.12 (-1.84, 2.07)	0.91/0%
2.7 Upper body strength	4	155	SMD (IV, Random, 95% CI)	0.43 (0.11, 0.75)	0.009/0%
2.8 Lower body strength	4	191	SMD (IV, Random, 95% CI)	0.19 (-0.20, 0.58)	0.34/43%
2.9 HRQoL – General	6	343	SMD (IV, Fixed, 95% CI)	0.41 (0.19, 0.62)	0.0002/0%
2.10 HRQoL - FACT-G	4	214	MD (IV, Random, 95% CI)	9.32 (-0.94, 19.57)	0.07/91%
2.11 HRQoL - FACT-B	4	532	MD (IV, Random, 95% CI)	2.77 (-2.60, 8.14)	0.31/52%
2.12 Physical well-being	7	456	SMD (IV, Random, 95% CI)	0.27 (0.02, 0.51)	0.03/42%
2.13 Mental/emotional well-being	8	511	SMD (IV, Fixed, 95% CI)	0.24 (0.06, 0.41)	0.008/28%
2.14 Fatigue	8	833	SMD (IV, Random, 95% CI)	-0.21 (-0.45, 0.04)	0.10/58%
2.15 Self-esteem	6	345	SMD (IV, Random, 95% CI)	0.21 (-0.14, 0.56)	0.23/60%
2.16 Depression	3	198	SMD (IV, Fixed, 95% CI)	-0.40 (-0.68, -0.12)	0.006/17%

Table 2.8.4 Summary of findings; analysis 3: aerobic and resistance exercise combined interventions vs. control

Outcome	Trial N	Sample N	Statistical Method	Effect Estimate (95% CI)	p-value/I^2
3.1 Cardiorespiratory fitness	8	346	SMD (IV, Random, 95% CI)	0.32 (-0.16, 0.81)	0.19/76%
3.2 Mass (kg)	5	237	MD (IV, Fixed, 95% CI (kg))	-4.10 (-7.65, -0.55)	0.02/0%
3.3 BMI (kg/m^2)	4	230	MD (IV, Fixed, 95% CI (kg/m^2))	-1.78 (-3.17, -0.38)	0.01/0%
3.4 Percentage Body Fat	5	230	SMD (IV, Random, 95% CI)	-0.25 (-0.60, 0.11)	0.18/38%
3.5 Waist circumference (cm)	3	187	MD (IV, Fixed, 95% CI (cm))	-1.03 (-4.84, 2.78)	0.53/0%
3.6 Hip circumference (cm)	3	187	MD (IV, Random, 95% CI (cm))	1.16 (-9.64, 11.97)	0.83/91%
3.7 Upper body strength (kg)	4	141	SMD (IV, Random, 95% CI)	0.53 (-0.44, 1.50)	0.28/86%
3.8 Physical well-being	3	98	SMD (IV, Random, 95% CI)	1.21 (0.01, 2.41)	0.05/84%
3.9 Mental/emotional well-being	3	98	SMD (IV, Random, 95% CI)	0.27 (-0.68, 1.23)	0.57/78%
3.10 Fatigue	5	273	SMD (IV, Random, 95% CI)	-0.72 (-1.40, -0.04)	0.04/81%
3.11 Self-esteem	3	99	SMD (IV, Random, 95% CI)	0.17 (-0.81, 1.16)	0.73/78%
3.12 Depression	4	225	SMD (IV, Fixed, 95% CI)	-0.39 (-0.70, -0.08)	0.01/36%
3.13 Anxiety	3	143	SMD (IV, Random, 95% CI)	-0.96 (-1.31, -0.61)	<0.001/0%
3.14 Interleukin-6	3	113	SMD (IV, Fixed, 95% CI)	-0.14 (-0.52, 0.24)	0.48/0%

Table 2.8.5 Summary of findings; analysis 3: resistance training only interventions vs. control

Outcome	Trial N	Sample N	Statistical Method	Effect Estimate	p-value/I^2
4.1 Mass (kg)	4	410	MD (IV, Fixed, 95% CI (kg))	-0.12 (-3.07, 2.82)	0.93/0%
4.2 BMI (kg/m^2)	4	343	MD (IV, Fixed, 95% CI (kg/m^2))	-0.32 (-1.47, 0.83)	0.58/0%
4.3 Percentage Body Fat	5	419	SMD (IV, Random, 95% CI)	-0.25 (-0.68, 0.18)	0.25/76%
4.4 Lean mass (kg)	4	398	MD (IV, Fixed, 95% CI (kg))	0.30 (-0.98, 1.59)	0.64/0%
4.5 Lower body strength	4	358	SMD (IV, Random, 95% CI)	0.70 (0.23, 1.16)	0.003/77%
4.6 Upper body strength	5	374	SMD (IV, Random, 95% CI)	0.84 (0.43, 1.25)	<0.001/68%
3.8 Physical well-being	4	379	SMD (IV, Random, 95% CI)	0.22 (-0.07, 0.51)	0.14/50%
3.9 Mental/emotional well-being	3	312	SMD (IV, Random, 95% CI)	-0.06 (-0.38, 0.26)	0.72/52%

Physical activity levels

Post-intervention follow-up values showed a significant moderate to large improvement in physical activity assessed via questionnaires compared with control in 982 trial participants (SMD 0.57; 95% CI 0.26, 0.89) (Analysis 1.1). There was a significant moderate to large effect when aerobic exercise only interventions were analysed separately (SMD 0.55; 0.21, 0.88). The two resistance training only trials that included follow-up physical activity data found no significant difference compared to controls (SMD 0.13; -0.23, 0.50). Similarly, the two aerobic exercise and resistance training combined trials found no significant effect (SMD 1.24; -0.28, 2.77). The four trials (all aerobic exercise only interventions) that included follow-up accelerometer (steps/day/week) physical activity data found no significant difference compared to controls (SMD 0.29, -0.29, 0.77) (Analysis 1.2). There was significant statistical heterogeneity when combining all studies in an SMD model. Subgroup investigation by intervention mode did not affect heterogeneity. Similarly, the presence of a psychological component did not alter the significance of the effect on physical activity (questionnaire-derived) or reduce heterogeneity to acceptable levels.

A sensitivity analysis of studies where the allocation concealment scored as low risk of bias versus unclear or with a high risk of bias was conducted. When three trials with unclear or high risk of allocation bias were removed the effect was moderate to large and remained significant (SMD 0.52; 0.05, 0.99).

Two trials for which we were unable to extract data also reported on physical activity (Saarto et al., 2011; Schmitz et al., 2009). Two of these studies reported no significant differences in physical activity in the intervention compared to the control group.

Cardiorespiratory fitness

A significant low to moderate improvement in post-intervention scores were found in the intervention group (412 participants) compared with the control group (322 participants) (SMD 0.30; 0.05 to 0.55) (Analysis 1.3). Similarly, a significant low to moderate effect was found when the aerobic exercise only interventions (SMD 0.30; 0.11, 0.49) were analysed separately, but no effect was found when aerobic and resistance exercise combined (SMD 0.32; -0.16, 0.81). There were insufficient resistance training only trials to analyse effects on cardiorespiratory fitness.

There was significant statistical heterogeneity when combining all studies in a SMD model. The omission of two trials (Sprod et al., 2010; Rahnama et al., 2010) that showed markedly different effects of physical activity compared to the other trials reduced heterogeneity to 0%. Subgroup investigation of aerobic exercise only interventions reduced heterogeneity to 0%. The inclusion of only trials that measured cardiorespiratory fitness directly via VO_2 max also reduced heterogeneity to 0% and remained significant (SMD 0.33; 0.11, 0.54). Subgroup analysis by presence of a psychological component reduced heterogeneity to 8% and remained significant (SMD 0.37; 0.10, 0.64).

A sensitivity analysis of studies where the allocation concealment scored as low risk of bias versus unclear or with a high risk of bias found that when seven trials with unclear or high risk of allocation bias were removed the precision of the effect estimate was improved and the effect was low to moderate and remained significant (SMD 0.32; 0.08 to 0.55; I^2= 11%).

Three trials for which we were unable to extract data also reported on cardiorespiratory fitness (Heim et al., 2007; Mefferd et al., 2007; Niemen et al., 1995). Mefferd et al. (2007) and Niemen et al. (1995) found a significant improvement in cardiorespiratory fitness in the intervention group compared to the control group. Heim and co-workers (2007) reported no significant improvement in either intervention or control groups.

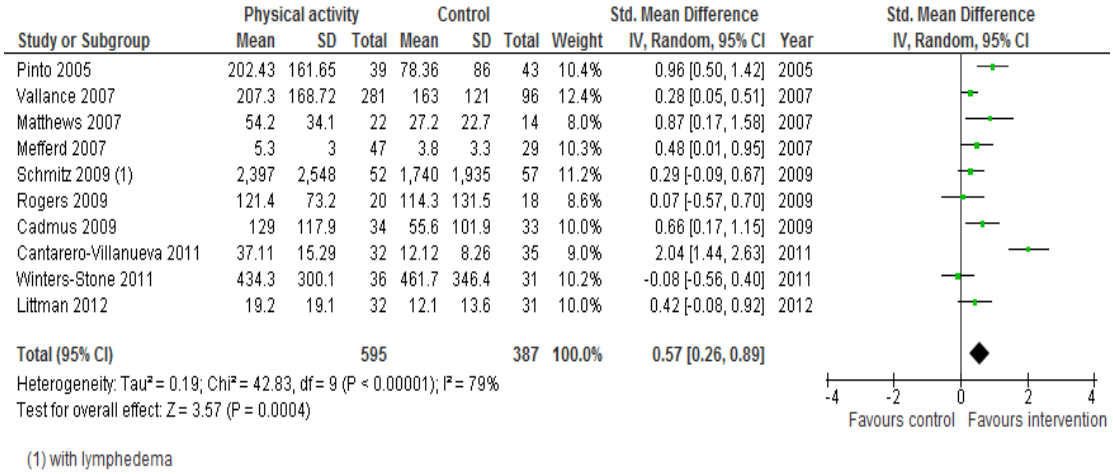


Figure 2.8.4 Forest plot: Physical activity vs. Control, analysis 1.1 Physical activity levels.

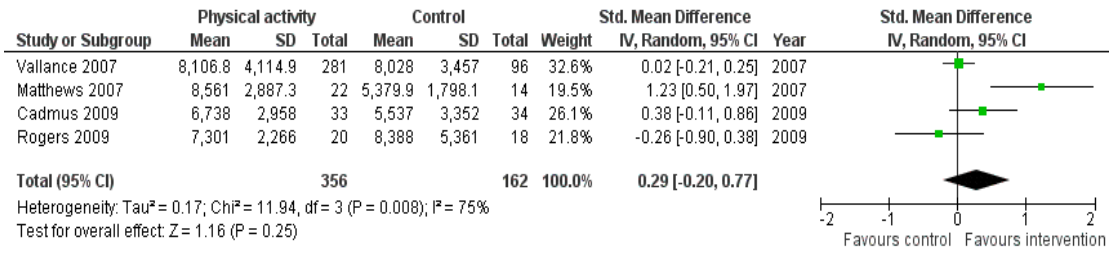


Figure 2.8.5 Forest plot: Physical activity vs. Control, analysis: 1.2 Physical activity (steps/day/week)

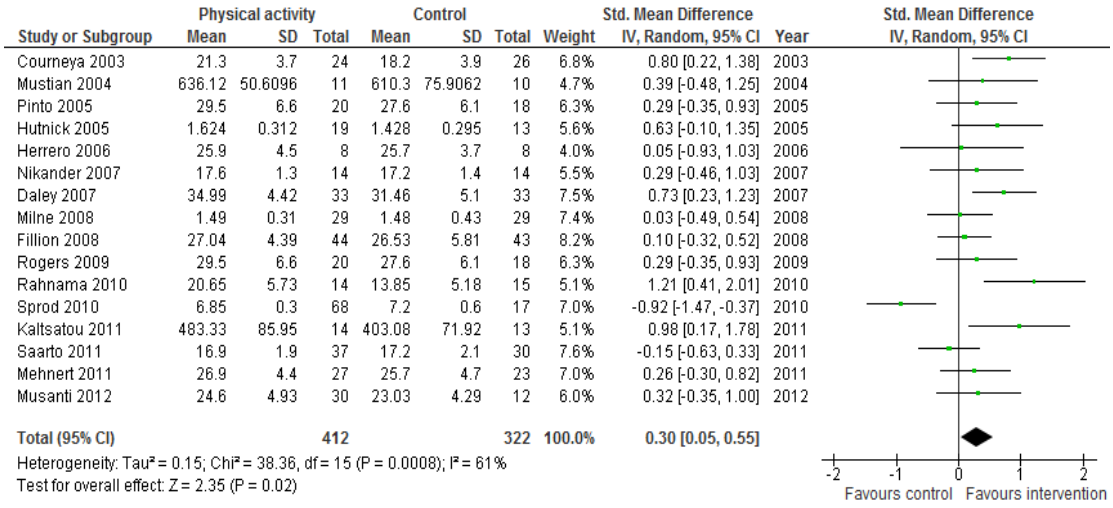


Figure 2.8.6 Forest plot: Physical activity vs. Control, analysis: 1.3 cardiorespiratory fitness

Anthropometric outcomes

There was no evidence of heterogeneity in the combined comparisons for mass, BMI, body fat %, lean mass, waist circumference or WHR. Evidence of heterogeneity was found only for hip circumference (I^2=82%). Post-intervention values showed no significant improvement in body mass compared with control in an analysis of 1103 trial participants (MD -1.61 kg; -3.38, 0.16 kg) (Analysis 1.4). Similarly, aerobic training only trials and resistance training only found no significant differences compared to controls (MD -1.62 kg; -4.80, 1.57 kg and MD -0.12 kg; -3.07, 2.82 kg, respectively). However, trials which combined aerobic training and resistance training significantly reduced body mass compared to controls (MD -4.10 kg; -7.65, -0.55 kg). There was no evidence of heterogeneity in the combined comparisons and comparisons by intervention mode. Subanalyses of only trials which included a psychological support component showed a significant reduction in body mass and 0% heterogeneity (MD -5.06 kg; -9.45, -0.68 kg). When 10 trials with unclear or high risk of allocation bias were removed in a sensitivity analysis the effect remained non-significant (MD -0.18 kg; -2.76 to 2.40 kg).

Physical activity was associated with a significantly reduced BMI (MD -0.4; -1.59, -0.13) compared to controls in 916 participants (Analysis 1.5). When the mode of training was considered, only the trials which combined aerobic training and resistance training reduced BMI significantly (MD -1.78; -3.17, -0.38). Analyses of six interventions that included a psychological support component also showed a significant reduction in BMI (MD -1.44; -2.62, -0.26). When six trials with unclear or high risk of allocation bias were removed the effect on BMI was not significant (MD -0.40; -1.33, 0.50).

Physical activity was associated with a low but significant reduction in body fat (SMD -0.15 %; -0.28, -0.03) and a non-significant effect on lean mass assessed via DEXA (MD 0.26 kg; -0.69, 1.21 kg) compared to controls in 1025 and 662 participants, respectively (Analysis 1.6 and 1.7, respectively). When intervention modes were analysed separately none had a significant effect on body fat or lean mass. Analysis of 10 trials that assessed body fat % by DEXA revealed a significant effect of physical activity compared to controls (MD -1.02; -1.97, -0.08). Analysis of two trials that assessed body fat % via BIA and SKF did not show a significant effect. Analysis of five trials consisting of a psychological support component showed a low to moderate significant reduction in body fat % (SMD -0.32; -0.57, -0.08), while the effect on lean mass in the two trials that measured lean mass included psychological support was non-significant (MD 0.08; -0.18, 0.34). The exclusion of eight and four trials with unclear or high risk of allocation bias for the sensitivity analysis of body fat % and lean mass, respectively, resulted in non-significant effects of physical activity compared to control.

No significant effect of physical activity compared to controls were found for waist circumference (n=380; MD -0.16 cm; -2.67, 2.35 cm), hip circumference (n=325; MD 0.56 cm; -5.30, 6.43 cm) or WHR (n= 196; MD -0.01; -0.03, 0.02) (Analysis 1.8 to 1.10). There were insufficient studies to compare the effects of intervention mode on each of these outcomes. In the hip circumference analysis one of the five trials reported a substantial increase compared to the other four. The removal of this trial reduced heterogeneity to 2%, but the effect on WHR remained non-significant after we removed this study from the meta-analysis. There were insufficient numbers of trials to conduct subanalyses of trials including a psychological support component for these anthropometric outcomes. The exclusion of trials with unclear or high risk of allocation bias did not change the effects of physical activity on these outcomes compared to control.

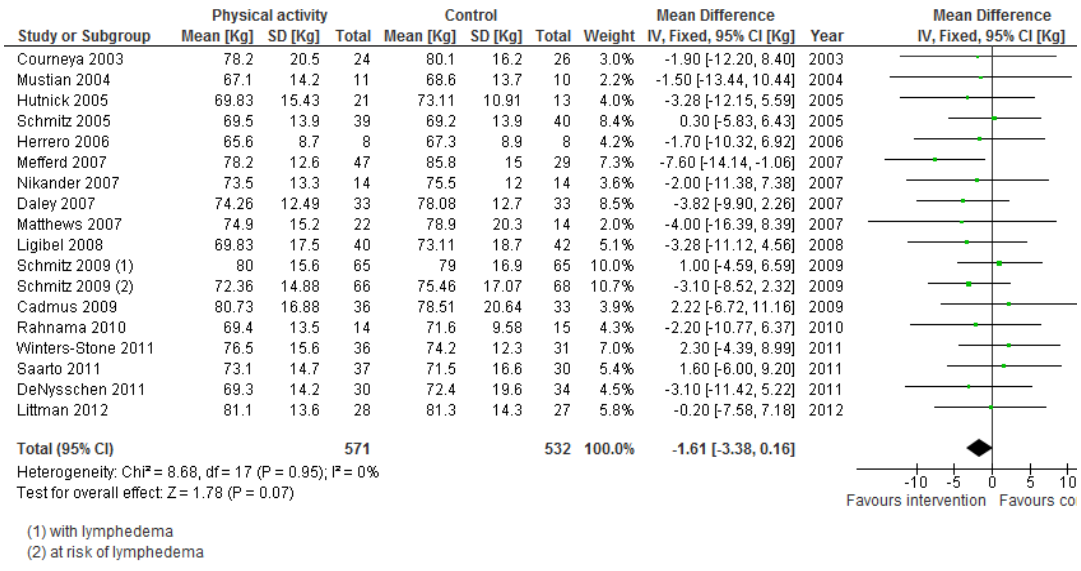


Figure 2.8.7 Forest plot: Physical activity vs. Control, analysis: 1.4 Mass (kg)

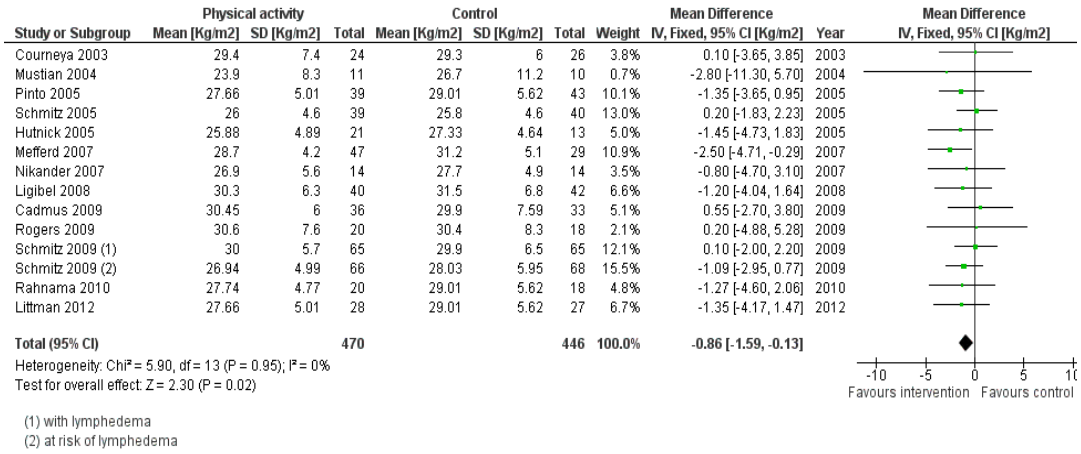


Figure 2.8.8 Forest plot: Physical activity vs. Control, analysis: 1.5 BMI (kg/m^2)

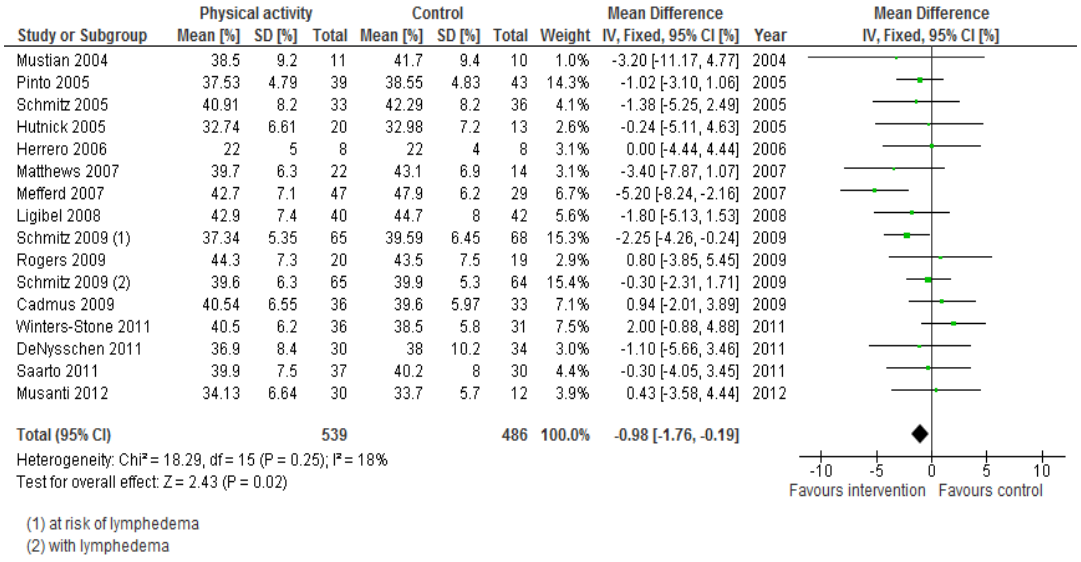


Figure 2.8.9 Forest plot: Physical activity vs. Control, analysis: 1.6 Body fat %

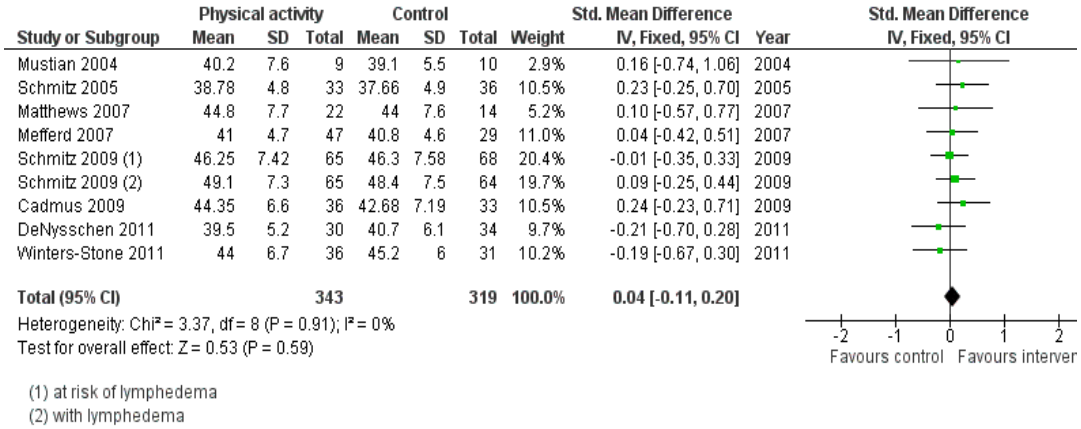


Figure 2.8.10 Forest plot: Physical activity vs. Control, analysis: 1.7 Lean mass

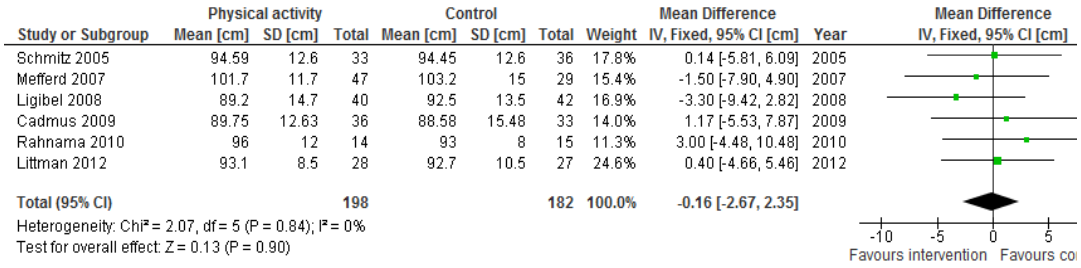


Figure 2.8.11 Forest plot: Physical activity vs. Control, analysis: 1.8 waist circumference (cm)

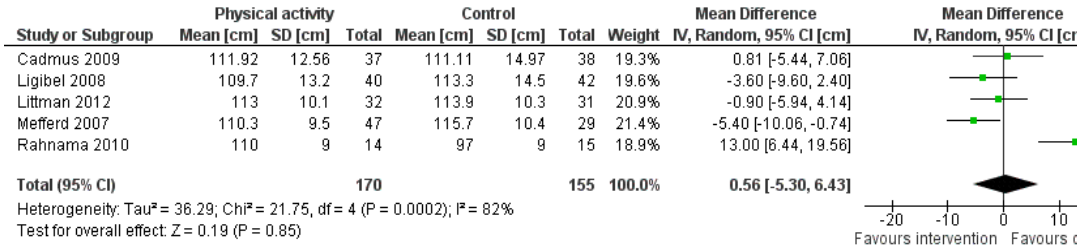


Figure 2.8.12 Forest plot: Physical activity vs. Control, analysis: 1.9 hip circumference (cm)

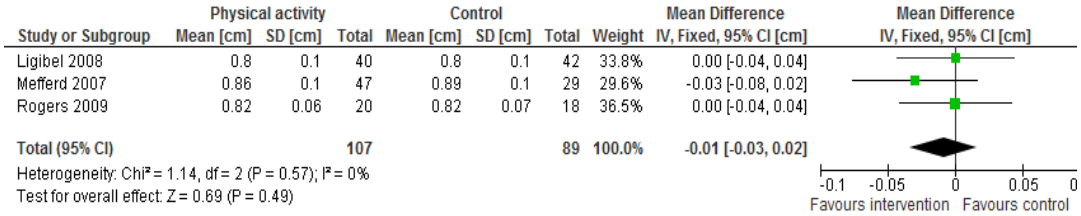


Figure 2.8.13 Forest plot: Physical activity vs. Control, analysis: 1.10 WHR

Upper and Lower Body Strength

Evidence of heterogeneity was found for both lower and upper body strength (I^2=72% and 76%, respectively). Physical activity was associated with a low to moderate significant effect on lower body and moderate to large effect on upper body strength (SMD 0.46; 0.12, 0.80 and SMD 0.61; 0.27, 0.94, respectively) compared to controls in 667 and 549 participants, respectively (Analysis 1.11 and 1.12, respectively). When analysing the four aerobic exercise only trials we found no significant effect on lower body strength (SMD 0.19; -0.20, 0.58; I^2=43%), while analysis including four of the aerobic exercise only trials revealed a low to moderate significant increase in upper body strength (SMD 0.43; 0.11, 0.75; I^2=0%).

Analysis of the four trials that consisted of combined aerobic and resistance exercise revealed no significant effect on upper body strength (SMD 0.53; -0.44, 1.50; I^2=86%), while there were insufficient trials to conduct analysis on lower body strength in these trials. Unsurprisingly, analysis of all resistance exercise only interventions had a moderate to large significant effect on lower and a large effect on upper body strength (SMD 0.70; 0.23, 1.16; I^2=77% and SMD 0.84; 0.43, 1.25; I^2=68%, respectively).

When trials that measured upper body strength using isometric hand grip dynamometers were analysed separately the effect remained significant but heterogeneity was reduced to 26%. However, analysing trials using chest/bench press to measure upper body strength did not alter the effect or heterogeneity. The method of measurement of lower body strength did not alter the effect or heterogeneity. There were only two trials and one trial that had a psychological support component in the upper body strength and upper body strength analysis, respectively. In the analysis of the two trials including a psychological support component, the effect of physical activity on upper body strength remained significant. The exclusion of trials with unclear or high risk of allocation bias did not alter heterogeneity or change the effect of physical activity on these outcomes compared to control.

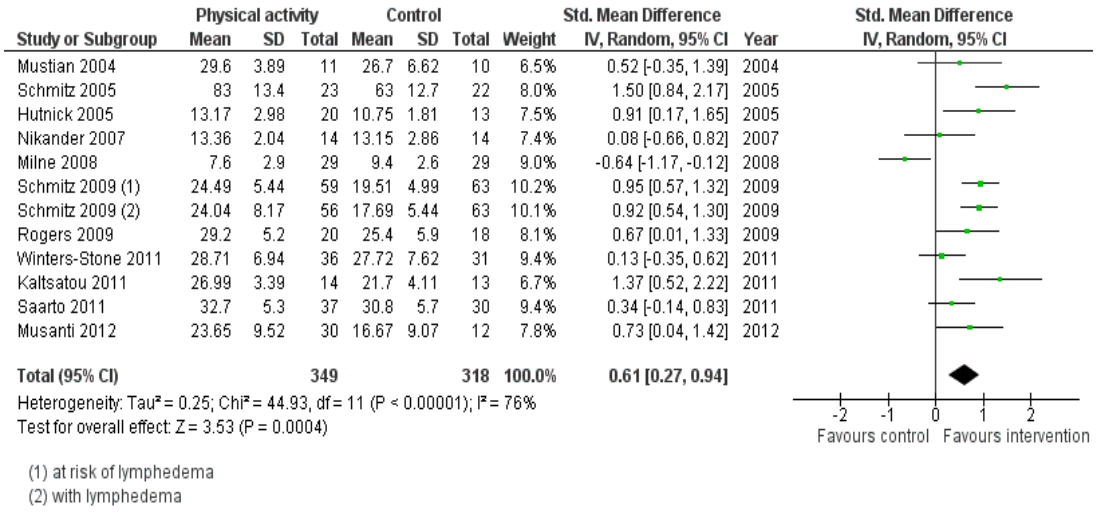


Figure 2.8.14 Forest plot: Physical activity vs. Control, analysis: 1.11 Upper body strength

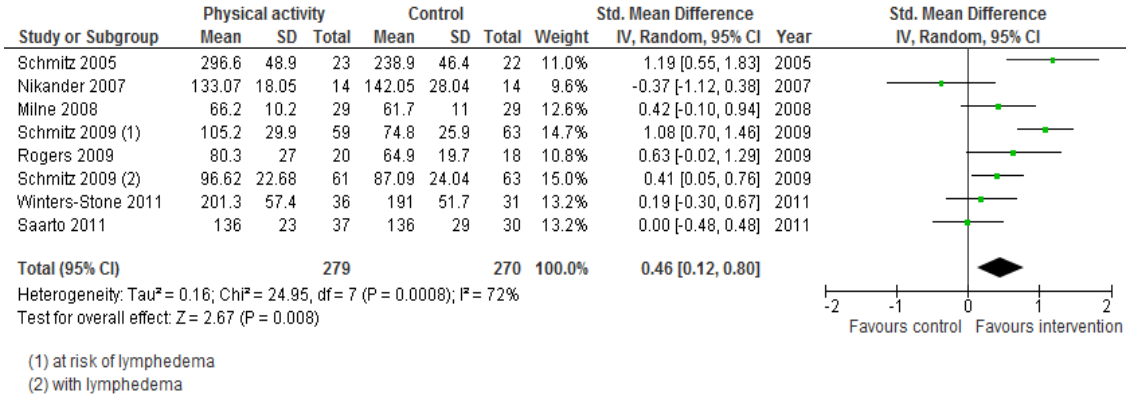


Figure 2.8.15 Forest plot: Physical activity vs. Control, analysis: 1.12 Lower body strength

Resting Systolic Blood Pressure

There was no evidence of heterogeneity for resting systolic blood pressure. Physical activity was associated with significantly reduced resting systolic blood pressure (MD -4.69 mmHg; -7.45, -1.93 mmHg) compared to controls in 108 participants (Analysis 1.13). As only three trials included this outcome a subgroup analysis was not performed. Two of the three trials were combined aerobic and resistance exercise interventions and one was an aerobic exercise only intervention. The two

combined aerobic and resistance exercise interventions had an unclear risk of allocation bias, while the other trial had a low risk.

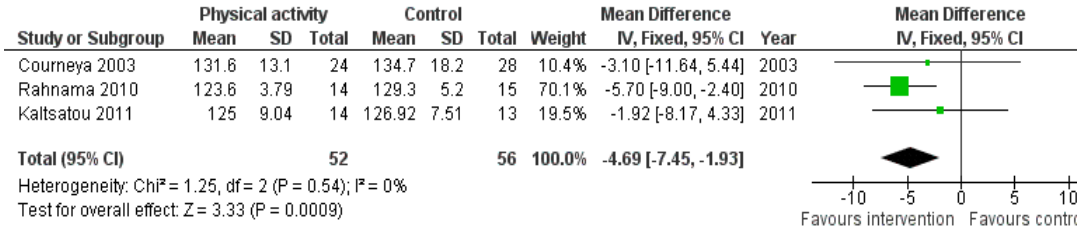


Figure 2.8.16 Forest plot: Physical activity vs. Control, analysis: 1.13 Resting systolic blood pressure

Health-related quality of life

There was evidence of substantial to considerable heterogeneity in general HRQoL, FACT-G, FACT-B and both physical and mental/emotional well-being, with heterogeneity ranging from 51% to 93%. Post-intervention values showed significant moderate to large improvements in general HRQoL compared with control in 657 trial participants (SMD 0.54; 0.22, 0.86) (Analysis 1.14). When aerobic exercise only interventions were analysed separately heterogeneity was reduced to 0% and there was a similar low to moderate significant effect (SMD 0.41; 0.19, 0.62). Analysis of two aerobic and resistance exercise combined trials resulted in a significant effect but substantial heterogeneity. There were insufficient resistance only trials for a subgroup analysis to be performed. In five trials with a psychological support component general HRQoL was significantly improved (SMD 0.43; 0.19, 0.67) compared to controls, with no statistical heterogeneity. The removal of three trials with a high or unclear risk of allocation bias did not alter the significance of the effect.

Separate analysis of HRQoL assessed via FACT-G and FACT-B questionnaires, did not reveal a significant improvement in HRQoL with physical activity, and showed considerable heterogeneity (I^2=90% and 93%, respectively) (Analysis 1.15 and 1.16, respectively). When FACT-G was analysed in the aerobic exercise only trials, the effect became significant (MD 4.51; 0.61, 8.41). However, this analysis was conducted in only three trials. Only the aerobic exercise alone trials had a psychological support component, therefore, the result of this subgroup analysis was the same as above. There were insufficient aerobic and resistance exercise and resistance only trials for a subgroup analysis to be performed. The removal of one trial with a high or unclear risk of allocation bias did not show a significant effect and revealed evidence of substantial heterogeneity. Of the five trials included in the FACT-B analysis four were aerobic exercise only trials. The removal of the one aerobic and resistance exercise combined trial did not alter the non-significant finding or reduce heterogeneity below substantial. Similarly, the inclusion of three of the five trials that included a psychological support component did not alter the effect or heterogeneity. All included trials were at a low risk of allocation bias.

Physical activity was associated with a low but significant improvement in physical and mental/emotional well-being (SMD 0.35; 0.22, 0.47 and SMD 0.16; 0.03, 0.29) compared to controls in 989 and 978 participants, respectively (Analysis 1.17 and 1.18, respectively). However, there was evidence of possibly substantial heterogeneity in both analyses (I^2=72% and 51%, respectively). The inclusion of aerobic exercise only trials did not alter the significance of the effect and lowered heterogeneity (I^2=42% and

30%, respectively). Aerobic and resistance exercise trials were associated with a significant effect for physical well-being but not for mental/emotional well-being, while resistance only trials showed a significant effect with no evidence of heterogeneity for physical well-being but no effect and substantial heterogeneity for mental/emotional well-being. Inclusion of trials that assessed these HRQoL domains using the FACT questionnaire, showed a significant effect on physical well-being but not for mental/emotional well-being, with evidence of substantial heterogeneity for both analyses. Analysis of the five trials with a psychological support component showed a significant effect on physical well-being for physical activity versus controls but with substantial heterogeneity, while analysis of six trials with this component revealed a significant effect on mental/emotional well-being but with moderate heterogeneity. Removal of four trials with a high or unclear risk of allocation bias did not alter the effect on physical well-being, but the removal of five trials due to the same reason produced a non-significant effect on mental/emotional well-being.

One trial for which we were unable to extract data also reported on HRQoL (Heim et al., 2007). This trial reported that physical activity resulted in an increase in HRQoL, although the trial also showed an increase in HRQoL in the control group.

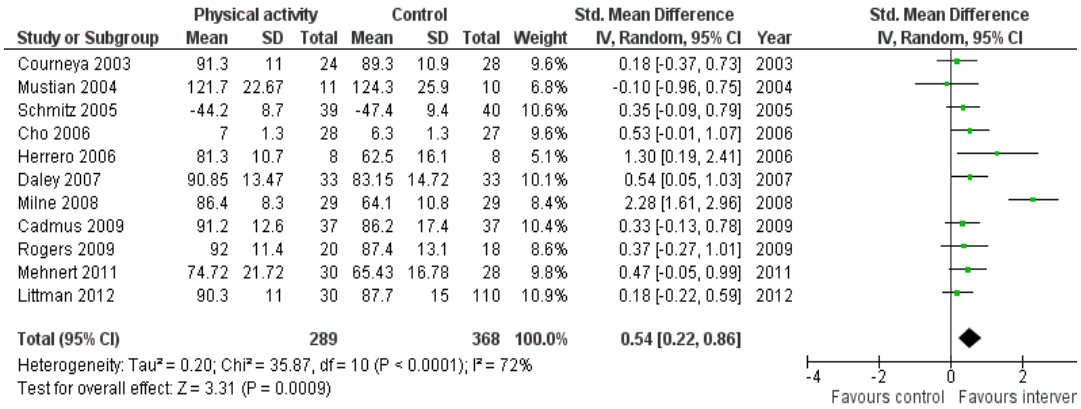


Figure 2.8.17 Forest plot: Physical activity vs. Control, analysis: 1.14 HRQoL – General

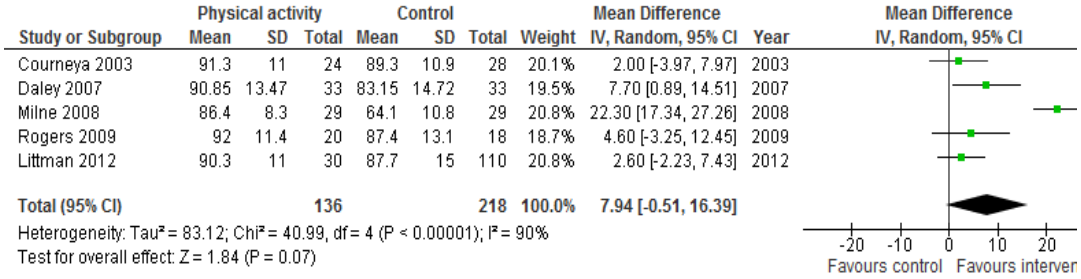


Figure 2.8.18 Forest plot: Physical activity vs. Control, analysis: 1.15 HRQoL - FACT-G.

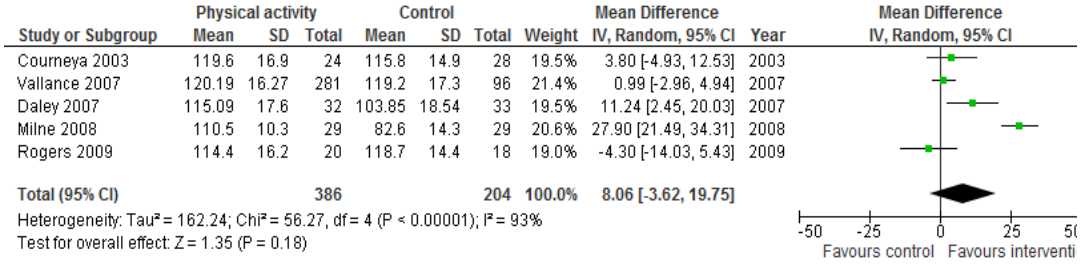


Figure 2.8.19 Forest plot: Physical activity vs. Control, analysis: 1.16 HRQoL - FACT-B

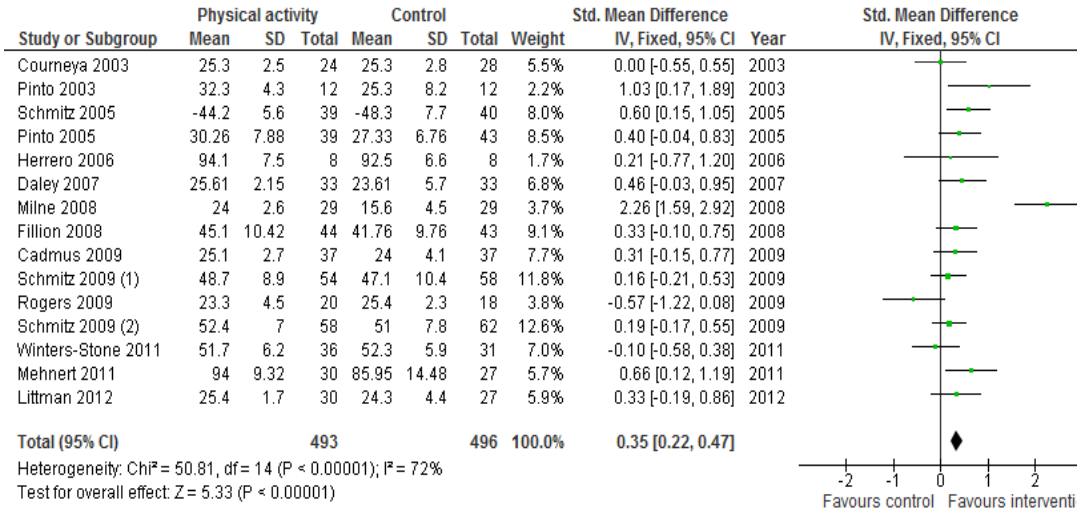


Figure 2.8.20 Forest plot: Physical activity vs. Control, analysis: 1.17 Physical wellbeing

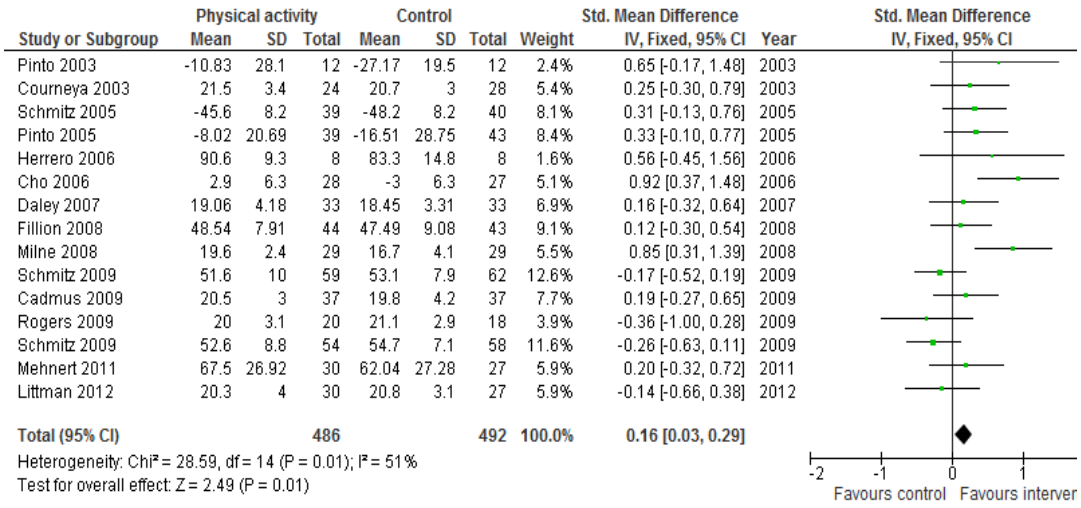


Figure 2.8.20 Forest plot: Physical activity vs. Control, analysis: 1.18 Mental/emotional wellbeing

Fatigue

There was evidence of considerable heterogeneity in the fatigue analysis (I^2=76%). Physical activity was associated with significant low to moderate reductions in fatigue (SMD -0.33; -0.59, -0.07) compared to controls in 1261 participants (Analysis 1.19). This effect was not evident when the aerobic exercise only trials were analysed separately (SMD -0.21; -0.45, 0.04; I^2=58%). Analysis of five trials that assessed aerobic and resistance exercise combined showed a moderate to large significant effect but with substantial heterogeneity (SMD -0.72; -1.40, -0.04; I^2=81%).

Analysis by fatigue instrument type, revealed no significant effect in the four trials using FACT-F, in three trials using PFS or in each of two trials using MFI and Schwartz fatigue scale. However, significant reductions in fatigue were shown only in trials using POMS and the QLQ-C30 to measure fatigue, with no evidence of heterogeneity in either analysis. Analysis including the five trials with a psychological component did not show a significant effect on fatigue, while the removal of five trials at a

high or unclear risk of allocation bias revealed a significant reduction in fatigue but evidence of substantial heterogeneity.

Among trials for which we could not extract data, one found a significant reduction in fatigue (Carson et al., 2009), one reported no group differences in fatigue (Payne et al., 2008), while one observed an initial improvement in both physical activity and control groups but found that over time the activity group improved slightly more while the control group became worse (Heim et al., 2007). Musanti (2012) assessed the change in clinically significant and non-significant fatigue in the total sample post-intervention, showing a significant reduction in clinically significant fatigue.

Psychological health outcomes and sleep

There was evidence of statistical heterogeneity across studies for the analyses of self-esteem and anxiety (I^2=50% and 57%, respectively), but not for depression (I^2=4%). Physical activity was associated with a low but significant increase in self-esteem compared to controls (SMD 0.29; 0.01, 0.57) in 441 participants (Analysis 1.20). However, the inclusion of aerobic exercise only trials changed the effect to non-significant (SMD 0.21; -0.14, 0.56 and SMD 0.17; -0.81, 1.16, respectively) and increased the heterogeneity across studies. No resistance exercise only trials were available in this analysis. The removal of one trial which showed a more marked effect on self-esteem (Musanti, 2012) reduced heterogeneity to 0%. Separate analysis by instrument type, found that two trials assessing self-esteem via BES and two by RSE, showed no significant effect on self-esteem. Inclusion of four trials with a psychological support component revealed low to moderate significant increases in self-esteem in the

physical activity group compared to controls (SMD 0.41; 0.16, 0.66) with no evidence of statistical heterogeneity. Including only studies with a low risk of bias for allocation concealment resulted produced a non-significant effect (SMD 0.20; -0.12, 0.53) and substantial heterogeneity.

We observed a significant low to moderate reduction in depression in the physical activity compared to the control group (SMD -0.41; -0.61, -0.21) in 454 participants (Analysis 1.21). This effect remained significant regardless of intervention mode, although, there were no resistance only trials included in the analysis. It was not possible to analyse according to the measurement instrument used because of an insufficient number of trials using the same instrument. The effect was not altered when the trials were analysed by the presence of a psychological support component or by the inclusion of only trials with a low risk of allocation bias.

There was a moderate to large significant reduction in anxiety in the group exposed to physical activity compared with the control group in 275 participants (SMD -0.64; -1.03, -0.26) (Analysis 1.22). However, this effect only remained significant when aerobic and resistance exercise combined trials were included (SMD -0.96; -1.31, -0.61). Examination by individual instrument assessing anxiety was not possible due to an insufficient number of trials using separate instruments. Similarly, only one trial that included a psychological support component was available in this analysis. Including only studies with a low risk of bias for allocation concealment resulted in a low to moderate effect that remained significant (SMD -0.26; -0.55, 0.03), although only one study was removed for this analysis.

Among trials for which we could not extract data, Payne et al. (2008) reported that exercise had no effect on depression, while two trials (Fillion et al., 2008; Heim et al., 2007) reported a combined anxiety and depression score. One trial (Heim et al., 2007) reported a significant reduction in the physical activity group but not the control group, while the other (Fillion et al., 2008) reported no effect.

Only three trials reported sleep disturbance, of which two assessed aerobic exercise only and one assessed yoga. No significant effect on sleep disturbance was found for physical activity compared to control (SMD -0.06; -0.56, 0.44) in 126 participants (3 studies; 2 aerobic exercise only and 1 yoga) (Analysis 1.23). The exclusion of the yoga trial or the inclusion of only trials with a psychological support component from the analysis did not alter the analysis. No subanalyses were performed on different measurement instruments due to inadequate number of trials. All three trials had a low risk of allocation bias. Among trials for which we could not extract data, one reported a large significant effect of exercise on sleep that was not present in the control group (Payne et al., 2008).

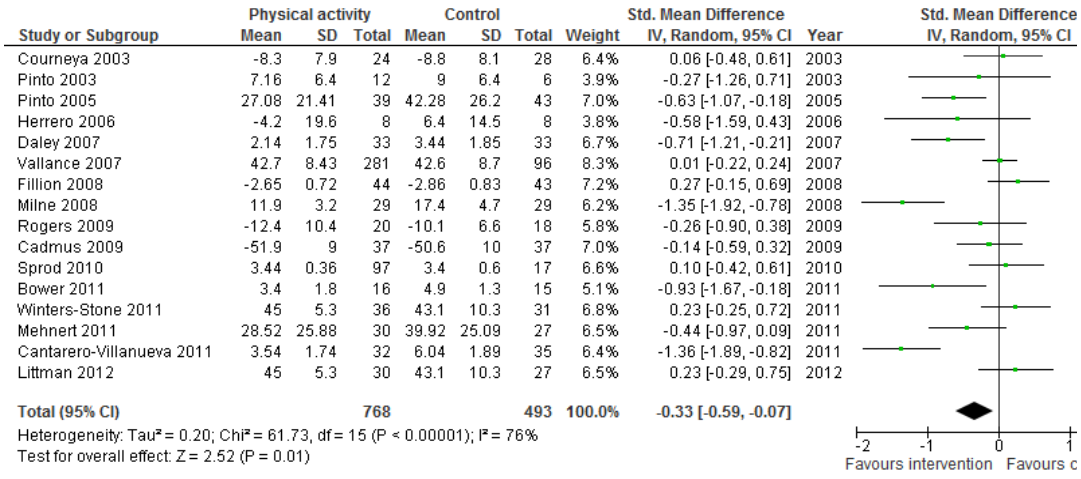


Figure 2.8.21 Forest plot: Physical activity vs. Control, analysis 1.19 Fatigue.

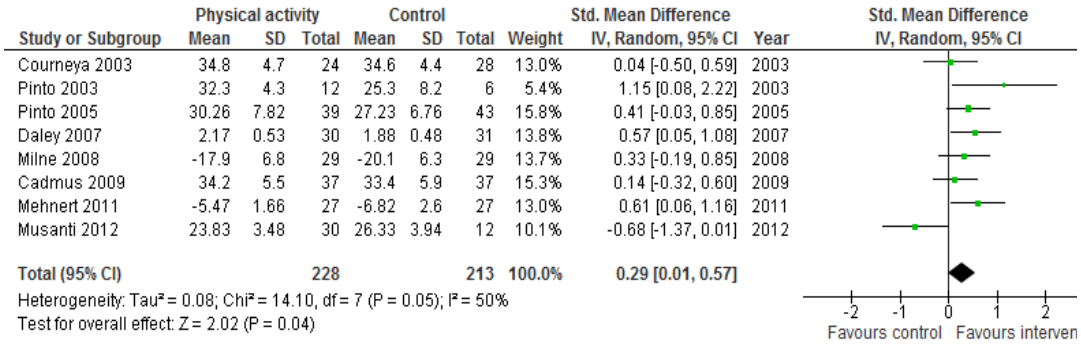


Figure 2.8.22 Forest plot: Physical activity vs. Control, analysis: 1.20 Self-esteem

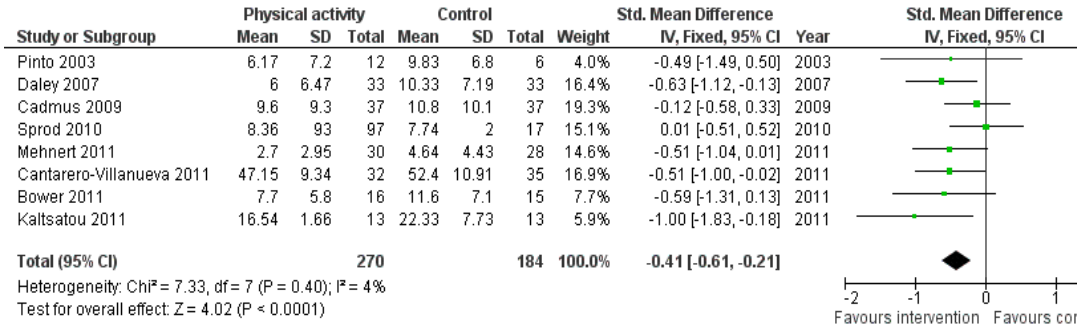


Figure 2.8.23 Forest plot: Physical activity vs. Control, analysis: 1.21 Depression

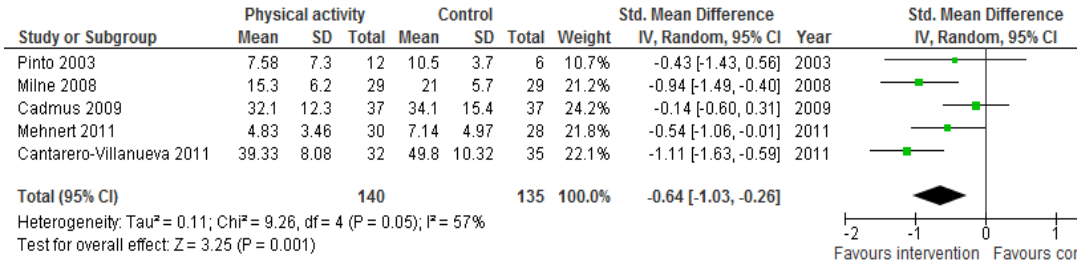


Figure 2.8.24 Forest plot: Physical activity vs. Control, analysis: 1.22 Anxiety

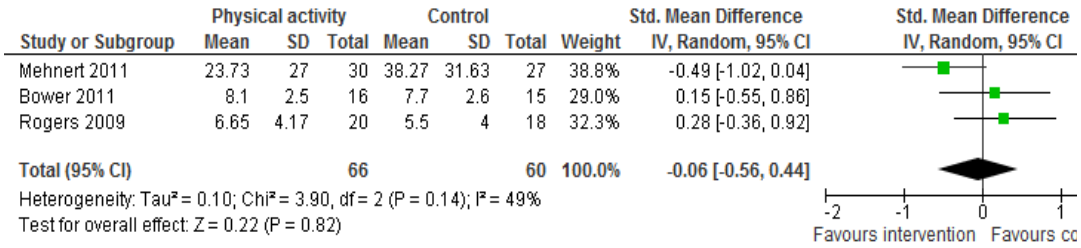


Figure 2.8.25 Forest plot: Physical activity vs. Control, analysis: 1.23 Sleep

Blood biomarkers

Nine blood biomarkers were included in the meta-analysis: insulin, glucose, HOMA, HDL-C, triglyceride, IGF-1, IGFBP-3, IL-6 and interferon-gamma (analysis 1.24 to 1.32). There was no substantial study

heterogeneity in five (glucose, HOMA, HDL-C, IGF-1 and IL-6) blood biomarkers.

In six trials, of which two assessed aerobic exercise, two assessed aerobic and resistance exercise combined and one each assessed resistance training and Tai Chi, physical activity was not associated with a significant reduction in plasma insulin (SMD −0.46; −1.12, 0.21; I^2=88%) compared to controls. The removal of one trial (Cadmus et al., 2009) that found a much more marked reduction in plasma insulin compared to the other five, reduced heterogeneity to 8%. Analysis by intervention mode, psychological support component or risk of allocation bias did not alter the effect. There was no effect in plasma glucose or HOMA in the group exposed to physical activity compared with the control group (SMD -0.11; -0.44, 0.22 and SMD -0.05; -0.34, 0.24, respectively) in 240 and 186 participants, respectively. The result did not alter in subgroup and sensitivity analysis. In two combined aerobic and resistance exercise trials and one aerobic exercise only trial, physical activity was associated with no effect on HDL-C or triglycerides (SMD 0.18; -0.26, 0.62 and SMD -0.17; -0.80, 0.45) compared to controls in 158 participants. Analysis of the combined aerobic and resistance exercise trials reduced heterogeneity in both analyses to 0% and resulted in a significant moderate reductions in triglycerides (SMD -0.50; -0.89, -0.10), but the effect on HDL-C remained non-significant. Similarly, analysis by psychological support component and risk of allocation bias did not alter the effect.

We observed no significant effect of physical activity on IGF-1 compared to controls (SMD -0.20; -0.54, 0.14) in 218 participants, although inclusion

of two aerobic exercise only trials resulted in a significant low to moderate reductions (SMD -0.41; -0.77, -0.05). In three trials, of which one each assessed aerobic exercise only, Tai Chi and resistance training only, physical activity was associated with a significant large reduction in IGFBP-3 (SMD -2.06; -3.99, -012). However, there was considerable heterogeneity in this analysis (I^2=95%), and removal of any one of the included trials did not reduce heterogeneity. None of the included trials consisted of a psychological component, while inclusion of two studies with a low risk of allocation bias did not alter the effects on either marker, but this was based on just two trials.

In four trials, three of which assessed combined aerobic and resistance exercise and one assessed Tai Chi, physical activity was associated with no significant reduction in IL-6 (SMD -0.05; -0.41, 0.30). There was no evidence of statistical heterogeneity. Separate analysis of the three combined aerobic and resistance exercise trials and two trials which included a psychological support component did not alter the effect. Three of the trials were at a high risk of allocation bias. In three trial, physical activity was associated with a significant large reduction in interferon-γ (SMD -1.35; -2.71, 0.02) compared to controls in 62 participants. There was evidence of substantial heterogeneity. However, the removal of a study (Herrero et al., 2006) that reported more substantial decreases than the other two studies reduced heterogeneity to 0%. Including only studies which combined aerobic and resistance exercise resulted in this result becoming non-significant, although two studies contributed to this analysis. Only one of the studies included a psychological support component and two trials were at a high risk of allocation bias.

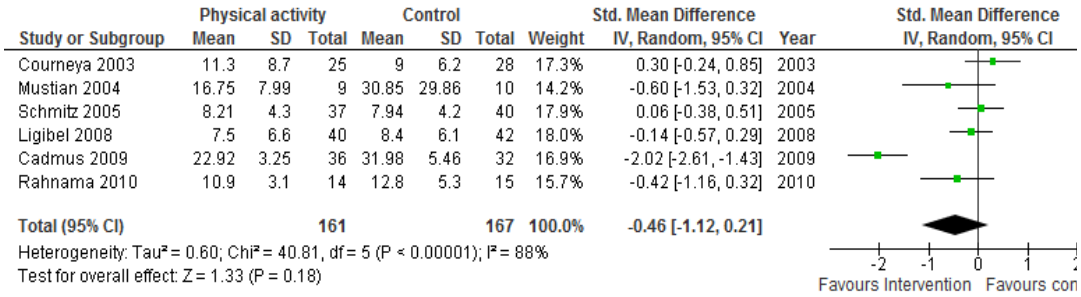


Figure 2.8.26 Forest plot: Physical activity vs. Control, analysis: 1.24 Insulin

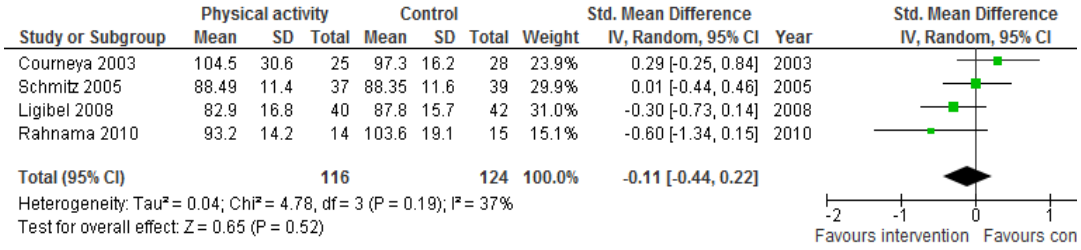


Figure 2.8.27 Forest plot: Physical activity vs. Control, analysis: 1.25 Glucose

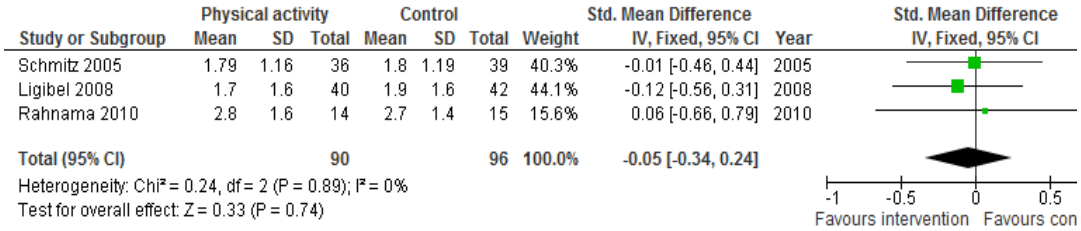


Figure 2.8.28 Forest plot: Physical activity vs. Control, analysis: 1.26 HOMA

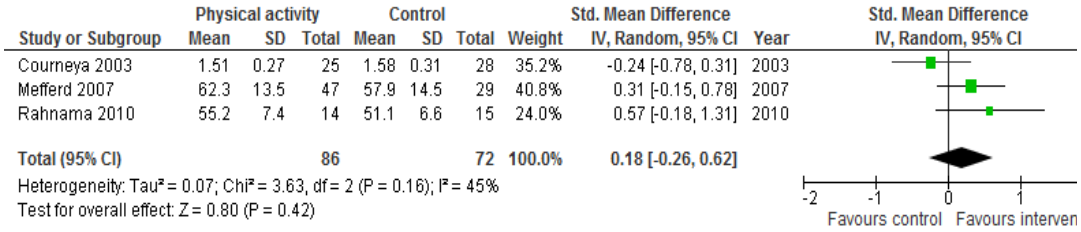


Figure 2.8.29 Forest plot: Physical activity vs. Control, analysis: 1.27 High Density Lipoprotein

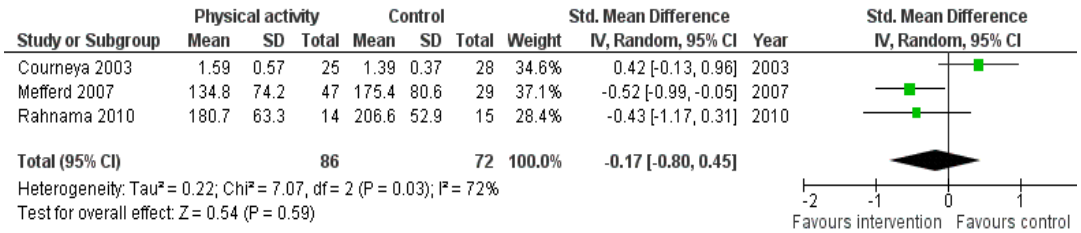


Figure 2.8.30 Forest plot: Physical activity vs. Control, analysis: 1.28 Triglyceride

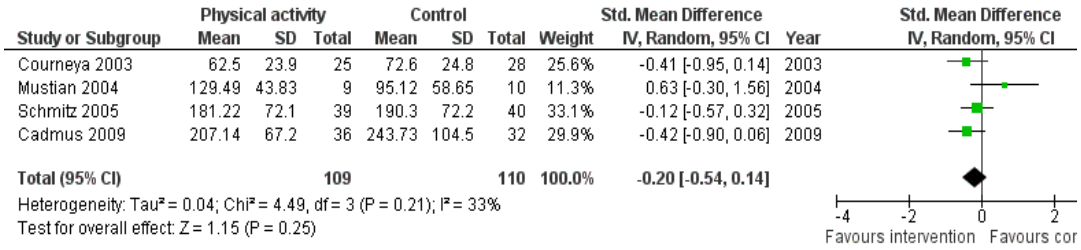


Figure 2.8.31 Forest plot: Physical activity vs. Control, analysis: 1.29 Insulin-like Growth Factor 1

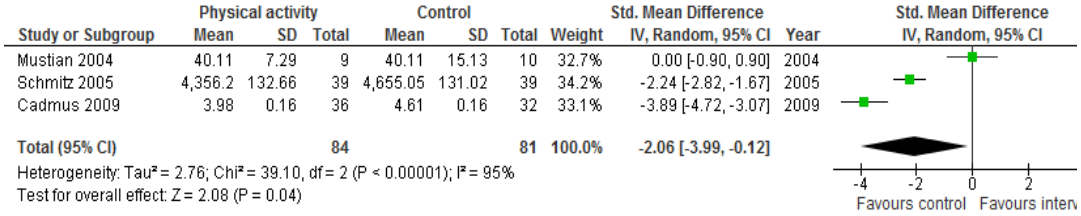


Figure 2.8.32 Forest plot: Physical activity vs. Control, analysis: 1.30 Insulin-like Growth Factor-Binding Protein 3.

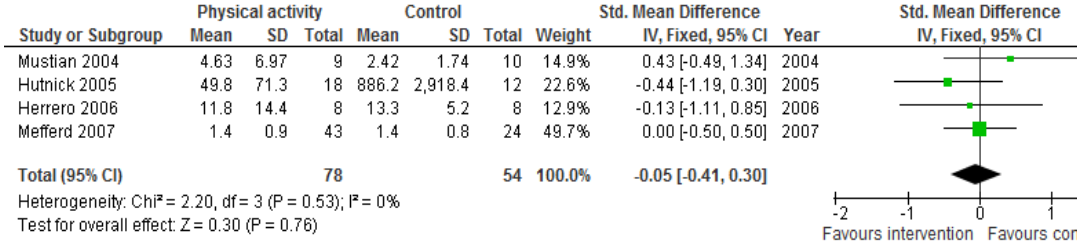


Figure 2.8.33 Forest plot: Physical activity vs. Control, analysis: 1.31 Interleukin-6

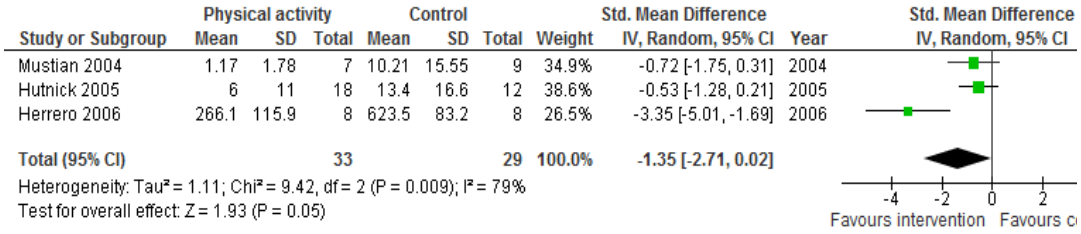


Figure 2.8.34 Forest plot: Physical activity vs. Control, analysis: 1.32 Interferon-gamma

Bone-related outcomes

There were an insufficient numbers of trials with common bone-related outcome measures to be included in the meta-analysis. BMD was assessed by DEXA in four trials (Cadmus et al., 2009; Rogers et al., 2009; Saarto et al., 2011; Winters-Stone et al., 2011), bone turnover was assessed in one trial (Winters-Stone et al., 2011) by serum osteocalcin and urinary deoxypyrodinoline cross-links (nmol/l) and in another trial

(Mustian et al., 2004) assessed bone resorption using serum levels of NTx, bone formation using serum levels of BSAP and bone remodeling index (BRI). Cadmus and colleagues (2009) found no significant difference between a physical activity intervention and control group for total BMD (g/cm^2) and BMC (g/cm). Rogers and co-workers (2009) reported no significant post-intervention differences in BMD of the femoral neck and lumbar spine between physical activity and control groups. Similarly, no significant differences between physical activity intervention and control groups were found for BMC of femoral neck, distal tibia or tibial shaft in another trial (Saarto et al., 2011). A resistance training only trial (Winters et al., 2011) found that the intervention group significantly preserved BMD of the spine compared to the control group, but reported no significant changes in total hip, greater trochanter and femoral neck in either intervention or control groups. The same trial (Winters et al., 2011) also found small but significant post-intervention increases in osteocalcin and a non-significant decrease in deoxypyrodinoline in the intervention group compared to the control group. Finally, Mustian et al. (2004) reported a non-significant increase in bone formation and a non-significant increase in bone resorption and a significant increase in bone metabolism (assessed via the BRI) was evident in the intervention group versus the control group.

2.8.5 DISCUSSION

2.8.5.1 Summary of main results

We included 34 trials with a total of 3,051 participants randomised to the physical activity intervention (n=1,720) or the comparison (n=1,319) groups. The results suggest that physical activity interventions compared

with control interventions have a significant positive impact on physical activity levels (assessed by questionnaire), cardiorespiratory fitness, BMI, body fat %, lower and upper body strength, systolic blood pressure at rest, general HRQoL, physical and mental/emotional well-being, fatigue, self-esteem, depression, anxiety, IGFBP-3 and interferon-γ. No significant effect of physical activity was found for accelerometer-derived physical activity levels, mass, lean mass, waist and hip circumferences, WHR, sleep disturbance, plasma insulin, glucose, HOMA, HDL-C, triglycerides, IGF-I or IL-6. The findings from bone-related outcome measures were inconclusive.

Analysis by intervention mode suggested that aerobic exercise only interventions compared with controls had a positive effect on physical activity levels (both questionnaire and accelerometer-derived), cardiorespiratory fitness, upper body strength, general HRQoL, physical and mental/emotional well-being and depression. Analysis of aerobic and resistance exercise combined trials suggested positive effects on mass, BMI, general HRQoL, physical well-being, fatigue, depression and anxiety. In the four resistance training exercise trials included in the analyses, only upper and lower body strength improved significantly.

The positive results must be interpreted with caution owing to the heterogeneity of physical activity interventions tested, the diversity of measures used to assess the various outcomes included and the risk of bias in many trials. Further research is required to investigate how to sustain positive effects of physical activity over time and to determine essential attributes of physical activity (mode, intensity, frequency,

duration and timing) for optimal effects on the outcomes included. The Summary of findings table 2.8.2, 2.8.3, 2.8.4 and 2.8.5 provides a summary of the main results.

2.8.5.2 Overall completeness and applicability of evidence

This systematic review included 34 trials, 31 of which were RCTs, one trial used a quasi-randomized design to allocate participants to treatment and two were non-randomised controlled clinical trials. These trials allocated 3,051 participants to either the physical activity or comparison groups. All trials included breast cancer survivors who had completed all treatment except for hormone therapy. Physical activity interventions tested in the trials varied greatly and included walking by itself or in combination with cycling and other aerobic activity, resistance training by itself or combined with aerobic activities, yoga or Tai Chi. A variety of outcomes were assessed using a wide range of measures.

The review draws upon studies from across the world, but predominantly from Europe and North America. The comprehensive search strategy obtained information from several electronic databases, citations through Web of Science and Scopus, grey literature through OPENGrey and review of reference list of other reviews in the field and reference lists of all included trials. There were no language or date restrictions in the search strategy. See search methods for identification of studies for details on the search strategy.

In terms of applicability of evidence, all of the trials included women with non-metastatic breast cancer, therefore, the results presented in this

current review cannot be generalised to metastatic breast cancer. Furthermore, many trials provided incomplete information on participant characteristics (staging, breast cancer treatment details, age, menopausal status, ethnicity, education level, annual income, physical activity history, mass and BMI) that would enable better comparisons between trials and assess generalizability of findings. Based on participant characteristics presented in trials, participants were generally white and with “University” level of education or higher. These characteristics would limit applicability of evidence to ethnic populations of breast cancer survivors and potentially those of a lower socioeconomic status. Furthermore, we only included the assessments made at the end of the intervention. Thus, it is unclear about how sustainable the positive effects of a physical activity intervention would be. The physical activity interventions varied greatly in their mode, frequency, intensity and duration of activity. These variations make it difficult to make informed decisions regarding the optimal prescription of physical activity, in terms of mode, frequency, intensity and duration of sessions and interventions.

The various outcomes were assessed using a diverse range of instruments with various degrees of precision, reliability and validity. Furthermore, reliance on self-report measures in some of the outcomes can open interpretation of findings to bias. There were differences in the effect of physical activity across trials using different outcome measurement instruments, which may undermine the results of the meta-analysis. In addition, none of the trials assessed the effects of physical activity on breast cancer recurrence and breast cancer-related and overall mortality within a RCT design. Finally, the trials provided no data on cost

or cost-effectiveness of physical activity interventions on outcome measures among breast cancer survivors.

2.8.5.3 Quality of the evidence

Results of the review need to be interpreted with caution owing to the risk of bias. All the trials reviewed were at high risk for performance bias because blinding of participants is not possible in physical activity interventions. Performance bias becomes accentuated in trials where participants are asked to provide self-report or subjective assessments of outcomes such as physical activity, HRQoL and psychological health outcomes. In addition, many trials were at high risk for detection bias, because outcome assessors were not blinded, were at high risk for attrition bias owing to inadequate handling of incomplete data, were at high or unclear risk for selection bias owing to inadequate random sequence generation or concealment of allocation to the intervention, and/or were at a high or unclear risk of other bias, mainly due to a lack of statistical power due to higher attrition rates than expected.

2.8.5.4 Potential biases in the review process

The strength of this review is the comprehensive search strategy that included a search of a number of electronic databases and review of reference lists of other reviews in the field and reference lists of all included trials. The comprehensive search strategy was designed and implemented to ensure the identification and retrieval of the maximum number of available published trials and trials in the grey literature. The search strategy also ensured no language restrictions. All trials published in non-English language were assessed for eligibility and, if eligible, had

data abstracted by native speakers of the language in which the trial was published. Only one non-English language trial (D'Attilio et al., 2007) could not be excluded by reviewing the title and abstract. This trial was translated by a native speaker (Italian) and did not meet eligibility criteria.

Despite a comprehensive literature search, it is possible that this current review may be at risk of publication bias. We prepared funnel plots to assess publication bias for follow-up values of physical activity, cardiorespiratory fitness, mass, BMI, body fat %, upper body strength, HRQoL-general, physical wellbeing, mental/emotional wellbeing and fatigue (see Figure 2.8.35 as an example; see appendix H for all funnel plots). Visually these figures showed there may be some slight asymmetry indicating that there is some publication bias in this area of research. We did not complete funnel plots for all outcomes, because too few studies contributed to some outcome measures. It is important to note that funnel plot asymmetry can result from reasons other than publication bias, such as selective outcome reporting, poor methodological quality leading to inflated effects in smaller less precise studies, true heterogeneity (i.e. size of effects differs according to study size, different populations or differing intensities of intervention), artefactual (i.e. where sample variation leads to an association between the effect estimate and its standard error) and random error (i.e. chance).

It is possible this review missed some potentially eligible trials in the grey literature. It is unclear whether the addition of trials only in the grey literature would have a significant impact on the results, given that trials reported only in the grey literature tend to have small sample sizes and

inconclusive results (McAuley et al., 2000). Furthermore, we corresponded with and requested additional data from seven trial authors (Carson et al., 2009; Daley et al., 2007; Heim et al., 2007; Mefferd et al., 2007; Niemen et al., 1995; Payne et al., 2008; Saarto et al., 2011), and only one of the trials authors (Daley et al., 2007) were able to provide additional data. The inability to obtain additional data from these trials resulted in an incomplete analysis and reduced the robustness of the meta-analysis. In addition, only the author assessed the eligibility of trials for this review, which may have increased the risk of selection bias.

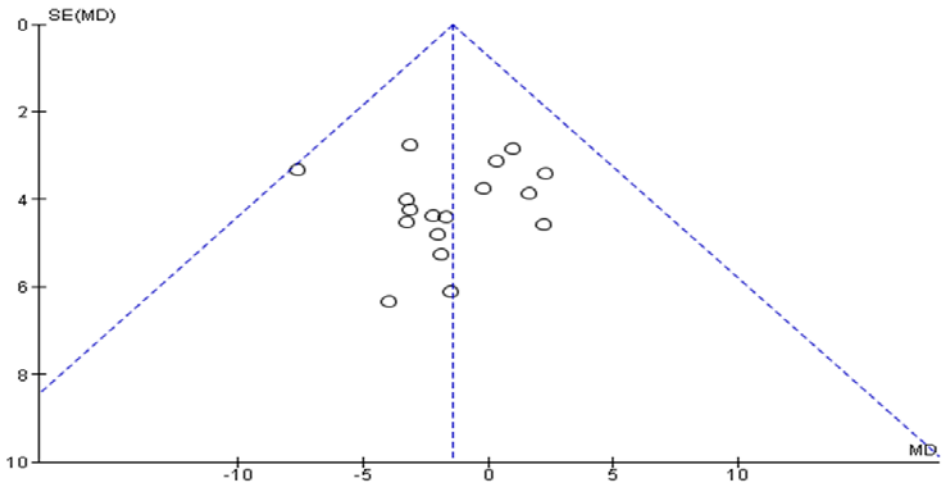


Figure 2.8.35 Funnel plot for analysis 1.4; Mass, all physical activity interventions vs. controls. The funnel plot shows evidence of possible publication bias due to a lack of symmetry (i.e. no inverted funnel shape).

2.8.5.5 Agreements and disagreements with other studies or reviews

Similar to this current review, in a meta-analysis of physical activity interventions for cancer survivors, Fong et al. (2012) found that trials including breast cancer survivors were associated with improvements in upper and lower body strength, HRQoL, fatigue and depression. While in another recent meta-analysis, Speck and colleagues (2010) also found improvements in physical activity levels, cardiorespiratory fitness, mass,

BMI, body fat %, upper and lower body strength, overall HRQoL, fatigue and depression. In a recent Cochrane review (Mishra et al., 2012) of the effects of physical activity interventions on HRQoL of breast cancer survivors, found that physical activity compared to control led to significant improvements in global HRQoL, body image/self-esteem, emotional well-being, sleep disturbance, social functioning, sexuality, anxiety, fatigue and pain. However, these significant effects occurred at different follow-up periods. The results of the current review is similar to that of the three recent meta-analyses in that we also found that physical activity interventions compared with control interventions may have a significant positive impact on physical activity levels (assessed by questionnaire), cardiorespiratory fitness, BMI, body fat %, lower and upper body strength, systolic blood pressure at rest, general HRQoL, physical and mental/emotional well-being, fatigue, self-esteem, depression and anxiety.

However, this is the first systematic review to analyse only studies where breast cancer survivors were analysed separately to other cancer survivors and includes all outcomes assessed in breast cancer survivors.
Unlike the current review, two meta-analyses (Fong et al., 2012; Speck et al., 2010) also found reductions in IGF-I. Both this current review and Fong and colleagues (2012) used the same four trials in this analysis, while Speck did not include one of the trials used in this current analysis (Mustian et al., 2004). However, Fong et al. (2012) used only the difference between the change scores for physical activity and control groups for one (Mustian et al., 2004) of the four trials included, instead of the follow-up means for both groups that was used for this current review. The use of the change values for one trial in Fong and co-workers (2012)

led to a more favourable result than the result reported in this current analysis. In Mustian et al. (2004) the physical activity group reduced their IGF-I more than the control group; however, because there was an imbalance in the IGF-I levels of the physical activity intervention compared to the controls, the follow-up values of the physical activity group were still below that of the controls. Raised levels of IGF-I have been proposed as a possible mechanism that may increase the risk of developing breast cancer and recurrence (Lynch et al., 2011). Therefore, a significant reduction in IGF-I by physical activity could potentially imply a lower risk of recurrence. However, given the low number of studies investigating this outcome and the conflicting results, suitably powered RCTs are required to establish the effects of physical activity on IGF-I and the impact of IGF-I on risk of recurrence.

We found significantly increased IGFBP-3 with physical activity interventions compared to controls, a finding which contradicts Speck et al. (2010). However, there was a difference in the eligibility criteria of studies which led to different trials being used in the analysis of this outcome. The role of IGFBP-3 on the risk of recurrence is conflicting, with some studies reporting lower risk with increased levels (Allen et al., 2005), while others reported lower risk with reduced levels (Yu et al., 1998; Goodwin et al., 2002a). Similar to the current review, both Fong et al. (2012) and Speck et al. (2010) found no significant positive effects of physical activity compared to controls on plasma insulin, glucose or HOMA. As in the current review, Speck and colleagues (2010) also found no significant positive effects on triglycerides and HDL-C. We found mixed results for the analysis of the two cytokines included in this analysis (IL-6

and interferon-γ. Similarly, Speck and co-workers (2010) found no significant effect of physical activity on immune parameters. Although the cancer treatment received is associated with pronounced immune deficiency and blood immune function is positively associated with progression-free and overall survival (Fairey et al., 2005), the effects of physical activity on immune parameters in post-treatment breast cancer requires further investigation.

Differences between this current review and previous reviews may be a result of the different eligibility criteria used for the current review (exclusion of trials with patients undergoing treatment, patients with metastatic disease or involving patients with cancers other than breast cancer and the inclusion of trials that assessed outcomes other than quality of life). In addition, this current review also included more recent trials not included in the other two reviews.

2.8.6 CONCLUSIONS

This current systematic review finds that physical activity interventions compared with control interventions have a significant positive impact on physical activity levels (assessed by questionnaire), cardiorespiratory fitness, BMI, body fat %, lower and upper body strength, systolic blood pressure at rest, general HRQoL, physical and mental/emotional well-being, fatigue, self-esteem, depression, anxiety, IGFBP-3 and interferon-γ among breast cancer survivors. Physical activity could be considered as an integral component for the management breast cancer survivors.

However, the positive results must be interpreted cautiously owing to the heterogeneity of physical activity interventions, measures used to outcomes and the risk of bias in many trials. Furthermore, a lack of understanding about important elements of physical activity interventions (mode, frequency, duration of sessions and interventions, intensity and settings) for optimal effects on physical, physiological, psychological and psycho-social outcomes would preclude informed decision-making in clinical settings and limit practical applicability of findings.

No evidence of effect was found for accelerometer-derived physical activity levels, mass, lean mass, waist and hip circumferences, WHR, sleep disturbance, plasma insulin, glucose, HOMA, HDL, triglycerides, IGF-I, IL-6 or bone-related outcomes. The lack of evidence may be due to few trials assessing these outcomes, small number of participants in trials measuring these outcomes and substantial heterogeneity between trials measuring these outcomes on the physical activity interventions implemented and measures used to assess the outcomes. Owing to these limitations, no conclusions can be drawn at this time regarding the effects of physical activity interventions on these outcomes.

From a practice perspective, it would be important to understand whether certain attributes of physical activity, such as intensity, duration and frequency of activity, have more or less optimal effects on particular outcomes among breast cancer survivors. In addition, an understanding of which modes are optimal for particular outcomes desired in breast cancer survivors. For example, elucidation of the optimal mode of physical activity (aerobic exercise alone, resistance exercise alone or aerobic and

resistance exercise combined) for decreasing BMI or body fat % in overweight post-menopausal breast cancer survivors would be valuable, and could potentially improve recurrence-free and overall survival.

Further research is required to investigate whether the effect of a physical activity intervention can be maintained beyond the active intervention period, and if so, how to sustain changes in physical activity behaviours and positive effects of physical activity on important breast cancer-related outcomes. Empirical evidence is also needed to determine the optimal follow-up period from the end of the intervention. In addition to this, the effects of physical activity outcomes needs to assessed longitudinally in order to investigate effects on breast cancer recurrence and breast cancer-related and overall mortality with a RCT design. More research is needed to determine optimal prescription of physical activity (mode, intensity, frequency, duration, setting) for breast cancer survivors for optimal effects on breast cancer-related outcomes. Due to problems with the heterogeneity of measurement instruments used in physical activity trials which make comparisons of findings between trials extremely difficult, more consistency is needed when measuring breast cancer-related outcomes. When assessing the validity of measurement tools used in trials, researchers need to carefully consider within the context of breast cancer survivors.

CHAPTER THREE: AIMS AND HYPOTHESES

The principle aims of the present project were to:

1. Assess the amount of physical activity undertaken by NHSBSP attendees, their levels of awareness of the role of physical activity and overweight/obesity in breast cancer risk and awareness of whether they engaged in sufficient amounts of physical activity.
2. To explore the physical activity levels in women at different stages of breast cancer pathway, that is, during breast screening (i.e. pre-diagnosis of breast cancer), during chemotherapy and within one year post-breast cancer treatment (breast cancer survivors).
3. Investigate the effects of a six-month home-based physical activity intervention on physical activity levels, mass and BMI, HRQoL, insulin resistance and blood lipid profiles of breast cancer survivors.
4. Examine the effects of a home-based physical activity intervention focused on the cardiorespiratory fitness of breast cancer survivors.

For each of the above aims the following hypotheses were made:

1. NHSBSP attendees were predicted to perform low levels of physical activity, have poor awareness of the role of physical activity and overweight/obesity on breast cancer risk and poor awareness of whether they engaged in sufficient amounts of physical activity.
2. We hypothesised that breast cancer patients undergoing chemotherapy would have the lowest levels of physical activity levels of the three participant groups, while breast cancer survivors who had completed treatment were expected to have lower physical activity levels than the NHSBPS attendees.

3. We predicted that breast cancer survivors allocated to a six-month home-based physical activity intervention would increase physical activity levels, maintain mass and BMI, improve HRQoL, reduce glucose, insulin and insulin resistance, lower TC, LDL-C and TG and raise HDL-C concentrations compared to breast cancer survivors allocated to usual care.
4. We expected that hypothesised improvements in physical activity in breast cancer survivors allocated to the home-based physical activity intervention would in turn increase cardiorespiratory fitness (VO_2 peak) compared to usual care.

CHAPTER FOUR: METHODOLOGY

4.1 PARTICIPANTS

For the purposes of this PhD project a total of 309 volunteers were assessed for the included studies. Of these participants 188 were women attending breast screening and 121 were breast cancer patients. In the first study (see 5.1) data was derived from 188 NHSBP attendees. In study 5.2 data was also derived from 41 breast cancer patients undergoing chemotherapy and 80 post-treatment breast cancer patients, in addition to the NHSBPS attendees. Study 5.3 consisted of the 80 post-treatment breast cancer patients and study 5.4 included a subset of 32 of the same 80 breast cancer patients. The Centre for Disease Control and Protection (CDC, 2013) defines a breast cancer survivor as anyone who has been diagnosed with breast cancer, from the time of diagnosis through the balance of her life. We have used this term to describe the post-treatment breast cancer patient.

Each study within the project had local research ethics committee approval by Dudley Ethics Committee. All participants were given verbal and written information about the project and signed an informed consent according to the declaration of Helsinki (World Medical Association, 2000). Due to the specific requirements of each study, details about the eligibility criteria and participants are presented in the methods section of the respective studies. Similarly, given the different designs and data collection methods utilised in this current project, the procedures of each study will be described in their respective methods sections.

4.2 ASSESSMENTS

4.2.1. Anthropometry and body composition

Standing height was measured to the nearest 0.5 cm on a portable stadiometer (Seca 214 Road Rod, Seca gmbh & co. kg., Hamburg, Germany). Body composition was assessed by bioelectrical impedance analysis (BIA) using a Tanita BC-418 MA Segmental Body Composition Analyser, which incorporates eight tactile electrode (Tanita Corporation, Tokyo, Japan). Body composition was assessed in terms of body fat %, fat mass, fat free mass (FFM) and total body water. The specific device has a standard error of <3% when standard procedures are followed (Demura et al., 1999). Standard procedures aim at reducing fluctuations in the hydration status of participants. BIA assesses water and electrolyte content of different parts of body (Bolanowski and Nilsson, 2001). Thus, participants were asked to refrain from excessive fluid consumption the day before the assessment and were instructed to drink two pints of water one to two hours prior to the assessment. After the initial manual entry of gender, height and age, participants stood bare-footed on the analyser and held the handgrips provided until the body composition analysis was completed. Body mass was also measured via the Tanita analyser and was recorded to the nearest 0.1 kg. BMI ($kg \cdot m^2$) was calculated on the basis of measured height and mass (mass in kg multiplied by height in m squared).

4.3.2 Physical activity

The International Physical activity Questionnaire (IPAQ) is a standardized, culturally-adaptable questionnaire that measures the intensity and time of physical activity. It was developed to allow comparisons of physical activity

data to be made across different countries (Hallal et al., 2010). There are two versions of IPAQ, including IPAQ-short form (IPAQ-SF), which is generally suitable for population surveillance purposes, and the IPAQ-long form (IPAQ-LF), which is recommended for research activities (Bauman et al., 2009). The IPAQ-LF version was utilised in the current thesis and provides detailed and comprehensive information on daily activity habits done in four different domains, including occupational, transportation, gardening and housework (domestic) and leisure activities. The questionnaire also includes questions about time spent sitting as an indicator of sedentary behaviour. In each of the four domains the number of days per week and time per day spent in both moderate and vigorous activity are recorded. At work, during transportation and in leisure time, walking time is also included. Practical examples of culturally relevant activities of moderate and vigorous intensity are given. Physical activity undertaken by participants in these domains was recorded for the seven days prior to assessments. Individuals first indicated the number of days (or “none”) in which they engaged in different intensities of activity in each of the four contexts for more than 10 min. If a number of days was entered, individuals were then asked to specify the total time in hours and minutes usually spent in the activity on one of those days. For purposes of data analysis, time was converted to minutes.

For standardised evaluation of physical activity, the metabolic equivalent (MET) time was estimated. One metabolic equivalent was defined by Ainsworth et al. (2011) as the metabolic turnover of 3.5 ml oxygen per kilogram body mass per minute in males and 3.15 $ml \cdot kg^{-1} \cdot min^{-1}$ in females. The weighted MET minutes per week were calculated as duration ×

frequency per week × MET intensity, which were summed across activity domains to produce a weighted estimate of total physical activity from all reported activities per week (MET-min·wk^{-1}) (Craig et al., 2003). Using MET-min·wk^{-1} as a means to combine aerobic activities of different types and intensities into a single measure of amount of activity. The IPAQ physical activity categories allow the categorisation of individuals into those who are meeting the current recommended physical activity guidelines (i.e. a minimum of 150 min of moderate-intensity physical activity per week) and those who are not (Bull and the Expert Working Groups, 2010).

The low activity category includes individuals who do not meet the criteria for moderate and high activity categories, and therefore, are not performing the recommended amount of physical activity. The moderate activity category represents those meeting current recommended guidelines for physical activity, and identifies individuals performing five or more days of moderate-intensity activity and/or walking of at least 30 min per day, three or more days of vigorous-intensity activity of at least 20 min per day or at least five days of any combination of walking, moderate- or vigorous-intensity activities achieving a minimum of at least 600 MET-min·wk^{-1}. This minimum 600 MET-min·wk^{-1} is based on quantification of moderate-intensity physical activity as 3.0 to less than 6.0 METs. Therefore, an adult can achieve 600 MET-min·wk^{-1} by performing moderate-intensity physical activity (4 METs) for ~150 min per week. The high activity category comprises of individuals achieving at least seven days of walking, moderate- and vigorous-intensity activities and a minimum of a least 3000 MET-min·wk^{-1} or those accumulating at least

1500 MET-min·wk^{-1} by performing at vigorous-intensity activity on at least three days.

The concurrent validity of IPAQ-LF was originally assessed in 12 countries, including the UK, against accelerometer data (Craig et al., 2003). The IPAQ-LF showed moderate concurrent validity (Spearman's rho=0.33) when compared to accelerometer data with around four-fifths of all individuals being similarly classified by the IPAQ and accelerometer data when physical activity data was categorised, which is similar to other self-report physical activity questionnaires (Craig et al., 2003). The two modes of administration for IPAQ-LF are self-administration and telephone administration. Each of these modes has its own specific questionnaire, which can be freely accessed online at http://www.ipaq.ki.se. For the purposes of the current study the self-administration version of the questionnaire was used (for IPAQ see Appendix P).

4.2.3 Health-related quality of life

Functional Assessment of Cancer Therapy-Breast (FACT-B) is a 36-item compilation of questions subdivided into four primary HRQoL domains, including physical well-being (PWB; 7-items), social/family well-being (SWB; 7-items), emotional wellbeing (EWB; 6-items) and functional well-being (FWB; 7-items), and a disease specific domain, which in this case was the "additional concerns for breast cancer" (breast cancer subscale; 9-items) (see Appendix Q). The four primary HRQoL domains are combined to provide a 27-item general HRQoL assessment (FACT-G). The total FACT-G score, which is the sum of the scores for the four HRQoL domains, is computed if the total item response is greater than

80%. The PWB, SWB, EWB, and FWB subscales and the FACT-G total score have a lowest possible score of 0. The highest possible score is 28 for the PWB, SWB, and FWB subscales; 24 for the EWB subscale; and 108 for the FACT-G total score. The total FACT-B score is calculated by the sum of FACT-G and breast cancer subscale scores. For these scales it is also possible to calculate a Trial Outcome Index (TOI). The TOI is the sum of the PWB, FWB and breast cancer subscale scores. The TOI endpoint provides an efficient summary index of physical/functional outcomes, particularly in clinical trials (Webster et al., 2003). Higher scores for the scales and subscales indicate better quality of life. See www.facit.org for full description and scoring. Social and emotional well-being domains are very important for HRQoL, which are not so likely to change quickly or dramatically over time or in response to therapy. The instrument has been validated in the breast cancer setting, with good internal consistency, reliability, patient acceptability and sensitivity to clinically significant change (Brady et al., 1997).

4.2.4 Blood biomarkers

Venipuncture blood samples were taken at baseline and at six months by hospital phlebotomists at the Phlebotomy clinic at Russells Hall Hospital. Blood sample analysis was performed at the biomedical laboratory in Russells Hall Hospital (see Appendix R). The blood samples were analysed for the following biomarkers.

Blood Lipids

Total cholesterol (TC), high-density lipoprotein (HDL-C) cholesterol and triglycerides (TG) were measured using the Vitros® 5.1 FS chemistry

system (Johnson and Johnson Inc., Langhorne, PA, USA). This system uses a slide, specific for each biochemical test, which is a multi-layered analytical element coated on a polyester support. A drop of the patient's serum/plasma is deposited on the slide and is evenly distributed by the spreading layer to the underlying layers. The fluid penetrates the reagent layer, which contains a dye that binds to the chemical to be measured from the sample. The binding results in a shift in wavelength of the reflectance maximum of the free dye. The colour complex that forms is measured by reflectance spectrophotometry. The amount of chemical-bound dye is proportional to the concentration of the chemical being measured in the sample e.g. calcium. For low-density lipoprotein cholesterol (LDL-C), the kit is a dual chamber package instead of a plate and contains ready to use reagents. The first reagent selectively eliminates non-LDL-C. When the second reagent is added surfactants dissociate cholesterol from cholesterol esters and proteins and promote the reaction with cholesterol esterase and cholesteroloxidase. Hydrogen peroxide is a by-product, which is then dyed and measured spectrophotometrically at 600nm.

Patients with increased levels of TG (>1.7 mmol/L), TC (>6.2 mmol/L), LDL-C (>4.13 mmol/L), decreased levels of HDL-C (<1.03 mmol/L) or receiving cholesterol-lowering therapy were characterised as dyslipidaemic (Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults, 2001). Patients with any of these measures were referred to the Head of Phlebotomy at the hospital and were invited for further testing.

Insulin Resistance

Plasma glucose was measured by the standardised procedure using the same VITROS® 5.1 FS chemistry system (Johnson and Johnson Inc., Langhorne, PA, USA) as described above and the same procedure as with cholesterol (but not LDL-C) was followed. Insulin was estimated from serum stored at -20°C. The method of detection is a solid phase two-site chemi-luminescence immunometric assay. The Immunolite 2000 insulin was used on the Immulite 2000 Analyser (Siemens Healthcare Diagnostics, Deerfield, IL, USA). This is a solid phase, competitive chemiluminescent enzyme immunoassay with an analytical range of 14.0-2,165 pmol/L. Insulin resistance (IR) was evaluated from fasting glucose and insulin using the HOMA of IR, and defined as HOMA ≥2.5, presence of diabetes mellitus or use of anti-diabetic medication (Radikova, 2003).

4.2.5 Cardiorespiratory fitness

Cardiorespiratory fitness was assessed in a random subset of the randomised patients (n=25, intervention; n=25, usual care) via an exercise tolerance test. All exercise tolerance tests were performed on a treadmill using the validated Bruce test protocol (Bruce et al., 1963). The Bruce test was started at 2.74 $km \cdot h^{-1}$ (1.7 $m \cdot h^{-1}$) and at incline of 10% for three minutes. At three minute intervals the incline of treadmill increased by 2% and speed increase to 4.02, 5.47, 6.76, 8.05, 8.85, 9.65, 10.46, 11.26 and 12.07 $km \cdot h^{-1}$ in each stage (10 stages in total), respectively. Ventilatory gas exchange was determined using a calibrated breath-by-breath system (Metalyzer 3B, CORTEX Biophysik GmbH, Leipzig, Germany) allowing continuous measurement of gas variables, including VO_2, VCO_2, minute ventilation (VE) and respiratory exchange ratio (RER). Moreover, during

the test heart rate was also monitored using a heart rate monitor and strap (Polar USA, Woodbury, NY). Testing was terminated when the participant reached voluntary exhaustion. The test was also discontinued if the participants showed signs of sudden paleness, change in heart rate, dizziness or cold sweat. Peak oxygen consumption was determined by taking the highest values during a 20-s period during the test. The assessment was conducted in controlled conditions in the cardiovascular laboratory of the Research and Development Unit of the hospital.

4.2.6 Blood Pressure

Prior to performing and three minutes after the exercise tolerance test, blood pressure (BP) was assessed three times on the brachial artery using a Datascope Accutorr Plus (Datascope, Montvale, NJ, USA), while the participant was resting in a seated position. Patients were given five minutes of sitting at rest before the first BP measurement was taken. The average of the three measurements is reported herein. Patients with a resting systolic BP of 140 mmHg or greater and/or diastolic BP of 90 mmHg or greater and/or receiving antihypertensive medication were characterised as hypertensive (Williams et al., 2004).

4.3 DATA MANAGEMENT AND ANALYSES

For all studies data were inserted in purpose-designed spreadsheets (Microsoft Excel™ 2008) and audited for accuracy weekly. All data was exported for analysis to the IBM® Statistical Package for Social Sciences® (version 20.0 for Windows, SPSS, Inc., Chicago, IL, USA). Due to the complexity of the project several different analyses were used. These analyses are described in detail in the respective studies.

CHAPTER FIVE: STUDIES

Study 5.1 has been accepted for publication in Health Promotion International.

Study 5.2 has been published in International Journal of Environmental Research and Public Health, 2014, **11**, pp. 5487-96.

5.1 Physical activity levels and awareness of breast cancer risk factors and sufficiency of physical activity in NHS breast cancer screening programme attendees

5.1.1 ABSTRACT

Introduction: This study aimed to determine the physical activity levels and awareness of the influence of physical activity and overweight/obesity on breast cancer risk among NHS breast screening programme (NHSBSP) attendees.

Methods: One hundred and eighty-eight (white British=95%; postmenopausal=80%) attendees completed a demographic and anthropometric data questionnaire, International Physical Activity Questionnaire (IPAQ) and awareness of breast cancer risk factors questionnaire. IPAQ data were reported as continuous measures (MET-min·week^{-1}) and as categorical variables (low, moderate and high activities).

Results: The highest median physical activity levels were reported in the domestic physical activity domain (756 MET-min·week^{-1}). Most participants were categorized as 'moderately active' (45%), while 30% were classified in the 'high activity' and 25% as 'low activity' categories. Almost a third of participants (30%) reported no leisure-time physical activity and 83% reported no vigorous physical activity. There was high awareness of the effects of physical activity (75%) and obesity (80%) on breast cancer risk.

No significant differences were found between physical activity categories and awareness that physical activity can reduce breast cancer risk ($p>0.05$). However, compared with moderate and high activity categories, participants in the 'low activity' category were significantly more likely to respond that they thought they achieved recommended physical activity levels ($p<0.05$).

Conclusions: Participants who are unaware of their inadequate physical activity levels may have a less positive intention to increase physical activity levels. Practical strategies aimed to increase knowledge of the recommended physical activity guidelines and facilitate the achievement of these guidelines may be required for NHSBSP attendees.

5.1.2 INTRODUCTION

In the UK, female breast cancer had the highest incidence rate of all cancers, with an average European age standardised (AS) rate of 124 cases per 100,000 population each year between 2007 and 2009 (ONS, 2012). Breast cancer is second only to lung cancer as the cause of death from cancer in UK women (European AS mortality rate=26.1 and 31.5 per 100,000, respectively) (ONS, 2012). Furthermore, the mortality of breast cancer increases proportionately with age (Walters et al., 2011).

Most risk factors associated with breast cancer are not readily amenable to intervention (Hill et al., 1997; Sprague et al., 2008; Begum et al., 2009), but lifestyle factors such as physical inactivity and postmenopausal obesity are potentially modifiable (Vainio et al., 2002; Lahmann et al., 2005; Begum et al., 2009). There is strong evidence for an inverse association between physical activity and breast cancer risk (Monninkhof et al., 2007;

Friedenreich and Cust, 2008; Lynch et al., 2011), with physical activity leading to an average relative risk reduction (RRR) of 25% when comparing the most physically active to the least active women (Lynch et al., 2011). Obesity is a risk factor for postmenopausal breast cancer, and obesity at the time of breast cancer diagnosis is associated with adverse outcomes in terms of lower quality of life and both disease-free and overall survival (Irwin et al., 2011). Greater breast cancer risk reduction has been found in those with a low (≤22 $kg \cdot m^2$) and moderate (22-25 $kg \cdot m^2$) body mass index (BMI) (RRR=27% and 24%, respectively) compared to those in the overweight (>25 $kg \cdot m^2$) and obese (>30 $kg \cdot m^2$) BMI ranges (RRR=18% and 1%, respectively) (Lynch et al., 2011).

Such evidence makes it imperative that concerted and targeted efforts are undertaken to enhance physical activity and reduce overweight/obesity in women to decrease the risk of breast cancer. According to most behavioural change theoretical models, the intention or motivation to change is one of the most important predictors of actual change (Bandura, 1986; Prochaska and DiClemente, 1983; Azjen and Fishbein, 1980). However, the intention or motivation to change is dependent on both the belief that a change in behaviour will reduce health risks and the extent to which an individual perceives his/her behaviour as 'unhealthy' (van Sluijs et al., 2007; Weinstein, 1980). Physical activity is a complex, multidimensional behaviour that occurs in a variety of different domains, which makes it difficult to assess the adequacy of one's own activity level. Therefore, individuals who are not sufficiently physically active may not perceive themselves as such, incorrectly believing themselves to be active. As much as 60% of adults who do not meet recommended

guidelines for physical activity may overestimate their own level (van Sluijs et al., 2007). Furthermore, 27% of individuals who are unaware they are not meeting recommended guidelines report a positive intention to change behaviour compared to 43% among those who accurately assess their inactivity (van Sluijs et al., 2007). Therefore, those who are unaware they are insufficiently active may be less likely to change behaviour and may be less susceptible to health promotion strategies. Hence, the rationale of this current study was to assess whether breast screening attendee's awareness of the effect of physical activity and overweight/obesity on breast cancer risk influenced their physical activity levels and whether participants were aware of the adequacy of their physical activity levels.

The UK NHS Breast Screening Programme (NHSBSP) currently reaches 75% of women between the ages of 47 and 73 y. Breast screening presents health professionals with many "teachable moments" that could be used to assess and raise, where necessary, awareness and promote changes in physical activity and weight management behaviours, and may offer an important opportunity to contribute to the reduction of the overall burden of breast cancer and other chronic non-communicable diseases (Fisher et al., 2007; Anderson et al., 2013). Despite this, at present, there is little data available regarding the levels of physical activity and awareness of breast cancer risk factors in NHSBSP attendees. Therefore, the aim of this study was to determine the amount of physical activity undertaken by women attending NHSBSP, their levels of awareness of the effects of physical activity and overweight/obesity on breast cancer risk and their awareness of whether they are sufficiently physical activity.

5.1.3 METHODS

Participants

Over a four week period (April-May, 2009) women attending routine breast screening were invited by the mammography practitioner to take part in this cross-sectional study. All women attending a single mobile screening unit in the Black Country (West Midlands, UK) were eligible. A total of 188 consecutive women attending the unit during the study period agreed to take part and provided informed consent after a verbal explanation. None of the women declined to participate. Ethical approval was obtained from Black Country NHS Research Ethics Committee in 2008.

Measures and procedures

After their routine screening mammogram, each participant completed two self-administered questionnaires; one was related to demographic characteristics while the other was a questionnaire designed by the research team, which assessed the participant's awareness of the role that physical activity and overweight/obesity can play in breast cancer risk. Participants responded whether they believed physical activity and overweight/obesity "increased risk", "decreased risk", had "no effect" on risk, or that they "do not know". Participants who responded that physical activity can result in a "decreased risk" of breast cancer were said to be aware that physical activity reduces breast cancer risk, and those who responded "increased risk" to the overweight/obesity awareness question were deemed to be aware that overweight/obesity can increase risk of breast cancer. In addition, after participants were informed of the current physical activity recommendation stating that "all adults should accumulate 30 min or more of moderate-intensity physical activity on at least five days

each week", participants were asked to respond "yes" or "no" to the following question; "do you think you do enough physical activity?" Participants were told that "enough physical activity" was defined as meeting the current physical activity recommendations. Participant's physical activity levels were assessed using validated long form International Physical Activity Questionnaire (IPAQ-LF) (Craig et al., 2003). IPAQ was administered during face-to-face interviews by the same specifically trained researchers (Hallal et al., 2010). Self-reported height and mass was used to calculate participants BMI.

Statistical analysis

Standard methods for the cleaning and treatment of IPAQ datasets were undertaken in accordance with IPAQ guidelines, which are available at http://www.ipaq.ki.se/scoring.pdf. Data that were normally distributed were reported as mean (±s), while data not normally distributed were expressed as median (interquartile range, IQR). Categorical data was expressed as number of responses/participants and percentages. The frequency of risk factors such as postmenopause, BMI 25 and over, non-parity, aged 30 and over at birth of first child, family history of breast cancer, previous or current HRT use and alcohol consumption was recorded.

For standardised evaluation of physical activity, the metabolic equivalent (MET) time was estimated. One metabolic equivalent was defined by Ainsworth et al. (2011) as the metabolic turnover of 3.5 ml oxygen per kilogram body mass per minute in males and 3.15 $ml \cdot kg^{-1} \cdot min^{-1}$ in females. The weighted MET-minutes per week were calculated as duration × frequency per week × MET intensity, which were summed across activity

domains to produce a weighted estimate of total physical activity from all reported activities per week (MET-min·wk^{-1}) (Craig et al., 2003). Using MET-min·wk^{-1} enables aerobic activities of different types and intensities to be combined into a single measure of amount of activity, and allows the categorisation of participant's physical activity. Physical activity categories were classified using the recommendations outlined in the IPAQ manual. Low activity represented individuals who do not meet the criteria for moderate and vigorous intensity categories (< 599 MET-min·wk^{-1}). Moderate activity represented those who reported at least five days of moderate or vigorous intensity activities achieving a minimum of at least 600 MET-min·wk^{-1}. This minimum 600 MET-min·wk^{-1} is based on quantification of moderate-intensity physical activity as approximately 4 METs. High activity represented achieving at least five days of moderate and vigorous intensity activities and a minimum of a least 3000 MET-min·wk^{-1}. The moderate activity category was used to identify those meeting current recommended guidelines for physical activity, that is, over a week, activity should add up to at least 150 minutes of moderate intensity activity in bouts of 10 minutes or more, e.g. 30 minutes on at least five days a week (Bull et al., 2010). In addition, BMI was recorded in a categorical score, classified into three levels "normal" (<25 kg·m^2), "overweight" (25–29.9 kg·m^2) and "obese" (≥30 kg·m^2).

Chi-square analyses were conducted to compare demographic and behavioural characteristics of sufficiently active (moderate and high activity categories) versus insufficiently active (low activity category) participants, and awareness (correct answer vs incorrect answer) of effects of physical activity and overweight/obesity on breast cancer risk.

Comparisons between awareness of physical activity and overweight/obesity roles in breast cancer risk and physical activity categories (low=insufficient; moderate-high=sufficient) and BMI categories ("normal" vs. either "overweight" or "obese") were analysed using chi-square tests. In addition, chi-square analysis was conducted to compare the response ("yes" or "no" or "don't know") to the question "do you think you do enough physical activity?" to self-reported physical activity categories (low, moderate and high). Odds ratios were calculated from 2 x 2 contingency tables for significant chi-square associations and was computed by OR=ad/bc. For example, the OR was the odds of a participant in the sufficient physical activity category answering "yes" to the "do you think you do enough physical activity?" question relative to the odds of a participant in the insufficient physical activity category answering "yes" to this question. Statistical analyses were performed using IBM® statistical Package for Social Sciences® for windows version 20.0; the level of significance was set at $p<0.05$.

5.1.4 RESULTS

Demographic details of participants are presented in Table 5.1.1. In summary, all of the women were aged 50 years or over (mean ± *s*; height = 1.6±0.1 m; mass = 70.7±14 kg; BMI = 26.9±5 kg·m^2) and the majority of the sample were postmenopausal (85%; n=146/182), white (95%; n=178/188) and British (77.5%; n= 146/188). Most of the women were categorised as overweight/obese (58%). There were a greater number of parous women (86%; n=160/188) in the sample and of these women most had one or two children (76%; n=121/188) and were aged between 21 and 30 years at the time of their first full term pregnancy (77%; n=122/188).

Table 5.1.1 Anthropometric, demographic, and lifestyle characteristics of the participants

	Number of Participants	Percentage
• BMI ($kg \cdot m^2$) (n=142):		
o Obese (BMI=≥ 30)	36	25
o Overweight (BMI=25-29.9)	46	32
o Normal (BMI=18-24.9)	60	42
o Underweight (BMI=< 18)	0	0
• Ethnic Origin (n=188):		
o White British	178	95
o Indian	3	2
o Black Caribbean	2	1
o White Irish	2	1
o One each of other White background, Pakistani, Chinese	3	2
• Menopausal status (n=182):		
o Premenopausal	13	7
o Postmenopausal	146	80
o Perimenopausal	15	8
o Unsure	8	4
• Number of Children (n=186)		
o Nulliparous	26	14
o 1-2	121	65
o 3 or more	39	21
• Age at birth of first child (n=160):		
o Under 20	20	13
o 21 to 25 years	73	46
o 26 to 30 years	49	31
o > 30 years	18	11
• Hormone Replacement Therapy (n=188):		
o Never	94	50
o Previously/Currently	94	50
• Family History of breast cancer (n=188):		
o Yes	27	14
o No	161	86
• Other conditions (n=188):		
o Hypertension	39	21
o Diabetes	9	5
o Angina	3	2
• Alcohol Intake (n=188):		
o Do not drink alcohol	55	29
o Drinks alcohol	133	71
• Drink type drank mostly (n=132):		
o Wine	108	82
o Beer or Spirits	24	18
• Smoking (n=188):		
o Currently/previously	23	12
o No	166	88
• Number of years smoking:		
o 1 to 15 years	3	13
o 16 to 35 years	14	61
o Over 35 years	6	26
• Number of cigarettes per day:		
o Under 10	12	52
o 11-20	11	48

There were an equal number (50%; n=94/188) of women who had previously or currently received hormone replacement therapy (HRT) as those who had never received it. Those with a history of HRT received it for a mean (*s*) duration of 80 (82) weeks. A minority (14%; n=27/188) of the sample had a family history of breast cancer. Over a quarter of women reported that they currently or have previously suffered from other medical conditions (27%; n=51/188), with hypertension (21%; n=39/188) being the most common. Almost three quarters (n=133/188) of the participants reported that they drank alcohol and a minority (12%; n=23/188) of the participants were current or ex-smokers.

The majority of participants (68%, n=128/188) reported three or more of the following risk factors, postmenopausal, BMI 25 and over, non-parous, aged 30 years and over at birth of first child, positive family history of breast cancer, previous or current HRT usage, alcoholic drinks consumer and insufficient physical activity. Only two participants had none of these risk factors.

The median and IQR for each of the IPAQ variables are presented in table 5.1.2. The greatest amount of physical activity was reported in the domestic physical activity domain (median, IQR=756, 1232 MET-min·wk^{-1}). There was a relatively low level of leisure time physical activity (median, IQR=330, 1020 MET-min·wk^{-1}). Almost a third of women (30%; n=57/188) reported no leisure-time activity. The majority of participants (83%; n=155/188) reported no vigorous physical activity. The application of the IPAQ criteria for categorical scores revealed that 25% (n=46/188) of the

participants were classified as low activity, while 45% (n=85/188) and 30% (n=57/188) were categorised as moderate and high activity, respectively.

Table 5.1.2 Median and IQR physical activity levels of women attending NHSBCSP

IPAQ continuous variables	Median	IQR
Overall physical activity (MET-min·wk^{-1})	1668	2305
Work physical activity (MET-min·wk^{-1})	0	0
Transport physical activity (MET-min·wk^{-1})	66	369
Domestic physical activity (MET-min·wk^{-1})	756	1232
Leisure physical activity (MET-min·wk^{-1})	330	1020
Walk physical activity (MET-min·wk^{-1})	396	974
Moderate physical activity (MET-min·wk^{-1})	963	1575
Vigorous physical activity (MET-min·wk^{-1})	0	0
Over physical activity (min)	420	560
Walk physical activity (min)	120	295
Moderate physical activity (min)	229	300
Vigorous physical activity (min)	0	0

We conducted chi-square analyses to compare demographic and behavioural characteristics of participants who were sufficiently active (moderate to high activity) versus those insufficiently active (low activity). Only family history was significantly different between the two physical activity categories (χ^2 (1) =4.05, p=0.04). This appeared to represent the fact that based on the odds ratio; the odds of participants being sufficiently active were 38.79 times higher in those with a family history of breast cancer compared to those with no family history. No significant differences were found between any other demographic or behavioural characteristic, when comparing sufficiently active participants with those insufficiently active. No significant differences in the above characteristics were observed when the high activity category was compared to a combined

low and moderate activity category or when those with a “normal” BMI were compared to those classified as either “overweight” or “obese”.

The majority (75%; n=136/188) of participants responded that they believed physical activity decreases the risk of breast cancer, while 25% believed that it either increases, had no effect, or did not know whether physical activity can influence breast cancer risk (see table 3). Similarly, most (80%; n=137/188) of the women believed that being overweight or obese increases the risk of breast cancer, only 20% (n=38/188) believed that being overweight or obese either decreases risk, had no effect, or did not know whether overweight/obesity affects breast cancer risk (see table 5.1.3).

We analysed differences in awareness across demographic and behavioural characteristics. There was a significant association between family history and awareness of physical activity effects on breast cancer risk (χ^2 (1)=7.33, p=0.005). Based on the odds ratio, the odds of participants being aware of effects of physical activity were 9.29 times higher in those with a family history of breast cancer compared to those with no family history. Similarly, family history was significantly associated with awareness of effects of overweight/obesity on breast cancer risk (χ^2 (1)=6.61, p=0.01). According to the odds ratio, the odds of participants being aware of effects of overweight/obesity were 7.67 times higher in those with a family history of breast cancer compared to those with no family history. No significant differences in awareness were observed between any other demographic or behavioural characteristics.

Table 5.1.3 Participant's awareness of physical activity and overweight/obesity and the risk of developing breast cancer, n (%)

	Decreases risk	Increases risk	No effect	Don't know
Physical activity (n=188)	136 (75)	3 (1)	14 (8)	29 (16)
Overweight/obesity (n=188)	3 (1)	147 (80)	5 (3)	29 (16)

Chi square analysis using three categories of physical activity status revealed no significant associations between awareness of the effects of physical activity and overweight/obesity on breast cancer risk. Similar findings were observed when the high activity category was compared to a combined low and moderate activity category. There was no association between BMI categories (normal and overweight/obese) and awareness of obesity as a breast cancer risk factor.

Table 5.1.4 Responses to the question "do you think you do enough physical activity?"

	Do you think you do enough physical activity?			
Physical activity Categories	**Yes**	**No**	**Don't Know**	**Total**
Low physical activity	33	6	3	42
Exp	25.2	10.9	5.9	
Moderate physical activity	51	21	16	88
Exp	52.8	22.83	12.37	
High physical activity	27	21	7	55
Exp	33	14.27	7.73	
Total	111	48	26	185

Exp=Expected assuming independence (null-hypothesis)
χ^2=11.65, df=4, p-value=0.02

Chi-square analysis using three categories of physical activity (low, moderate and high) revealed significant associations between physical activity categories and the response to the question "do you think you do enough physical activity?" (χ^2 (4)=11.65, p=0.02). Those in the low physical activity category were more likely to respond that they thought

they do enough physical activity, while conversely those in the high physical activity were more likely to respond that they thought they did not do enough physical activity (see table 5.1.4).

5.1.5 DISCUSSION

To the authors' knowledge, this current study is the only study that has assessed the levels of physical activity and awareness of the influence of physical activity and overweight/obesity on breast cancer risk amongst breast screening populations in the UK. Although, the majority of the women were categorised into the moderate and high physical activity categories (45% and 30%, respectively), a quarter of the women were classified in the low activity group. Moreover, a relatively large percentage (30%) of women reported no leisure-time physical activity and very few participants reported any vigorous physical activity (17%). In addition to this, the majority of participants (58%) were overweight/obese according to their self-reported BMI. Of the demographic and behavioural characteristics, only associations were found between physical activity levels and family history of breast cancer. Participants with a family history of breast cancer were more likely to be sufficiently active than those with no family history. The majority of participants were aware of the effects of physical activity (75%) and overweight/obesity (80%) on breast cancer risk. When comparing awareness across demographic and behavioural characteristics, significant differences in awareness were found only for family history of breast cancer. Those with a family history were more likely to be aware of the effects of physical activity and overweight/obesity on breast cancer risk than those with no family history. No differences in awareness of the effects of physical activity and overweight/obesity on

breast cancer risk were found between physical activity categories and BMI categories. However, significant associations were found between physical activity categories and whether participants thought they were doing enough physical activity. Participants in the low physical activity category were more likely to respond that they thought they were doing enough physical activity, and those in the high physical activity category were more likely to respond that they thought they were not doing enough physical activity.

The dominant physical activity reported by the participants was domestic physical activity in the current study. This type of activity has been consistently linked with reduced breast cancer risk (Friedenreich et al., 2002; Lahmann et al., 2005; Lynch et al., 2011). However, in the present cohort, the number of women who did not report any leisure-time physical activity was a concern. Research reveals that leisure-time physical activity can attribute to the largest reductions in breast cancer risk (Monninkhof et al., 2007; Friedenreich and Cust, 2008). Lynch and colleagues (2011) in a recent review of the epidemiological literature reported that greater decreases in breast cancer risk were observed with greater duration of recreational physical activity. In addition, there was also a low incidence of vigorous physical activity in this current study. Vigorous physical activity has been associated with a greater risk reduction in breast cancer compared to moderate physical activity (Gammon et al., 1998; Friedenreich and Cust, 2008; Lynch et al., 2011). Dallal and colleagues (2007) reported that long-term strenuous physical activity (>5 $h \cdot wk^{-1}$ per year) is inversely associated with both invasive and in situ breast cancer risk. Leitzmann and co-workers (2008) observed that vigorous intensity

physical activities almost entirely contributed to a reduction in breast cancer risk, although, these beneficial effects of vigorous physical activity were limited to those with a normal BMI (18-25 $kg \cdot m^2$). Our findings of a lack of reported leisure-time and vigorous physical activity in a relatively large number of participants suggests that these participants are not currently exposed to the possible greater breast cancer reductions associated with these forms of physical activity. In addition, a high prevalence of overweight/obesity suggests that the majority of our sample would benefit from both physical activity and weight management guidance to promote breast cancer risk reducing behaviours.

Although, the majority of the screening population were aware that physical activity reduces breast cancer risk and overweight/obesity increases risk, there were still a sizable percentage of women who responded “no effect” or “don’t know” that physical activity or being overweight/obese can influence breast cancer risk (24% and 19%, respectively). Despite this high awareness of the effects of physical activity and overweight/obesity on breast cancer risk, there was no association between the awareness of these factors and physical activity and BMI. Therefore, the participants who were aware that physical activity can reduce the risk of breast cancer were no more active than those who were unaware. Similarly, overweight/obese women were no more or less aware of overweight/obesity as a breast cancer risk factor. This finding is consistent with the general view that awareness and knowledge alone are insufficient for promotion and maintenance of long-term behavioural change (Carleton et al., 1996; Marcus et al., 2006; Williams et al., 2008).

Although, they do represent an important first step towards a future change in behaviour (Marcus et al., 2006; Ferrari et al., 2007).

Women with a family history of breast cancer were more likely to be sufficiently active and aware of physical activity and obesity/overweight effects on breast cancer risk than those without. There is evidence that most women with a family history of breast cancer are aware of their own increase in risk and, indeed, tend to overestimate this risk (Audrain-McGovern et al., 2003). In support of our finding that women with a history of breast cancer were more active than those without, Ochoa and colleagues (2010) found that women with a family history of breast cancer had twice the probability of performing more intense physical exercise. However, other studies (Townsend et al., 2013; Madlensky et al., 2005) in contrast have not shown differences in health behaviours between those with and without a family history of breast cancer.

The women in our sample who were aware of the benefits of physical activity but were not sufficiently active may not have been aware that their physical activities were low. We found that participants in the low physical activity category were significantly more likely to perceive that they were performing sufficient amounts of physical activity. This finding is consistent with previous research that has shown that adults who are not currently meeting recommended guidelines overestimate their own levels of physical activity (Ferrari et al., 2007). Participant's awareness of whether they were doing sufficient physical activity was poor regardless of physical activity category. This finding is perhaps unsurprising given that a recent survey reported that only 6% of men and 9% of women could correctly

define the minimum recommended targets, the majority underestimated (69% men and 68% women) or overestimated (25% men and 23% women) the amount of physical activity recommended (Townsend et al., 2012). Furthermore, evidence suggests that participants who are not aware of their inadequate physical activity level have a less positive intention to increase their level of physical activity than those who rate their own physical activity level as low (Ronda et al., 2001). People may only consider changing their behaviour when they consider their behaviour to be inappropriate and is potentially putting their health at risk, which may help to explain the findings that women with a family history of breast cancer engage in more intense exercise than women without a family history (Ochoa et al., 2010; Cavill and Bauman, 2004). Those at greatest risk of health problems may fail to recognise their inactivity and therefore, are unlikely to perceive a need to change and may be less susceptible to health promotion campaigns. Alternatively, some respondents with a high level of awareness and knowledge who do not engage in sufficient physical activity levels may lack the necessary skills or require additional information and/or support on how to make behavioural changes (Carleton et al., 1996). Therefore, strategies to increase that awareness of physical activity benefits may not be necessary; rather awareness of the recommended physical activity guidelines and the promotion of strategies that facilitate the achievement of these guidelines may be required.

This study has a number of limitations that need to be considered when reviewing these results. Self-report measures of physical activity which require participants to recall past activity, such as IPAQ, are a subjective means of estimating individual physical activity levels, and are reliant on

the individuals' ability to remember levels of exposure (Watkinson et al., 2010). Over reporting of physical activity, especially of time and intensity and activities in the occupational and domestic domains may be a problem in this type of assessment (Weinstein et al., 1998). There is evidence to suggest that up to 60% of adults who do not meet recommended guidelines for physical activity overestimate their own level of physical activity (van Sluijs et al., 2007).

The number of women categorised in the "moderate" and "high" physical activity categories were surprisingly high compared to the much lower levels of physical activity reported in the Health Survey for England in 2008 (Roth, 2009). Using the "moderate" category of the IPAQ to identify those meeting current recommended guidelines for physical activity may be troublesome. The creators of the IPAQ acknowledge challenges with interpreting these physical activity categories (Bauman et al., 2009). Respondents categorised as moderately active are those whose total physical activity exceeds 600 MET-min·wk¯1 or those who reported 30 min of "moderate" (4-MET intensity) activity or equivalent at least 5 days a week. This category is described as "moderate" in the IPAQ scoring protocol because it would be achieved by most adults through background activity, such as occupational activity, gardening and housework, and family care that adults accumulate daily. Bauman and colleagues (2009) recommend using the "high" IPAQ category to account for this limitation in using self-report total activity scores to identify those meeting physical activity recommendations. Use of the "high" category to identify those meeting current recommended guidelines for physical activity would have

brought the results in line with the findings of the Health Survey for England (Roth, 2009).

We used a self-designed questionnaire to assess participant's awareness of physical activity and overweight/obesity and the sufficiency of their physical activity. The two questions were not validated and therefore, may be at risk of response bias if there was a lack of comprehension on the part of respondents. The use of vague and ambiguous terms imposes a cognitive burden on respondents, and thus increase the risk of questions being interpreted idiosyncratically by respondents, which in turn can introduce a systematic bias into the questionnaire data (Sturgis and Smith, 2010). Systematic bias can lead to measurement error which may result in misclassification. Therefore, we attempted to avoid the use of vague and ambiguous terms in the two questions and explained the meaning of the questions to respondents before completion.

The use of self-reported BMI has been criticised as an inappropriate tool for precise measures of obesity prevalence (McAdams et al., 2007). The available literature consistently points toward an underreporting of mass and overreporting of height, leading to an underreporting of BMI (Ziebland et al., 1996; Nawaz et al., 2001; Connor Gorber et al., 2007; McAdams et al., 2007; Elgar and Stewart, 2008; Bes-Rastrollo et al., 2011). However, there is evidence that self-reported BMI values tend to overestimate measured BMI values at the low end of the BMI scale (<22 $kg \cdot m^2$) and underestimate BMI values at the high end, particularly at values > 28 $kg \cdot m^2$ (Stommel and Schoenborn, 2009). In this current study, it is likely that there were fewer participants with BMI values in the lower end of the

scale than the higher end, and considering the general trend in the literature towards an underestimation of BMI, it is perhaps more probable that our mean self-reported BMI represents an underestimation rather than an overestimation.

The ability to generalise our findings to the entire NHSBSP population is limited due to its relative small sample size and the use of a single mobile screening unit based at one site in the West Midlands. Currently, there is limited demographic data on breast screening attendees to compare our sample against, so it was not possible to assess how representative the sample was post-hoc. However, the BMI of this current sample was similar to self-reported BMI in a previous study of breast screening populations (Fisher et al., 2007) and the 58% prevalence of overweight/obesity in the current study was also close to the 60% of adult women in the West Midlands reported in The Health Survey for England in 2010 (Joint Health Surveys Unit, 2011).

Nevertheless, our findings can only be generalised to breast cancer screening attendees within the Black Country area of the West Midlands, UK. Future larger scale multi-site studies are required to confirm the findings of this current study.

5.1.6 CONCLUSIONS

To the authors' knowledge, this current study is the only study that has assessed the levels of physical activity and awareness of the influence of physical activity and overweight/obesity on breast cancer risk amongst breast screening populations in the UK. In this current study, a relatively

large number of women reported no leisure-time or vigorous physical activity which are important lifestyle choices to reduce the risk of breast cancer. Most of the participants were aware that physical activity can reduce breast cancer risk and overweight/obesity can increase risk, but no differences were found between awareness and physical activity and self-reported BMI levels. However, participants who performed low physical activity were unaware that they were not performing sufficient physical activity. Poor awareness of inadequate physical activity levels has been associated with less positive intention to change behaviour and increased physical activity levels. Therefore, this population may benefit from strategies aimed to increase awareness and knowledge of the recommended physical activity guidelines and facilitate the achievement of these guidelines.

5.2 Physical activity behaviour of women attending breast screening, receiving chemotherapy and post-breast cancer treatment; a cross-sectional study

5.2.1 ABSTRACT

Introduction: A lack of physical activity is a well-recognised risk factor in the development of breast cancer and evidence-based research on the impact of physical activity on breast cancer survival is consolidating. However, evidence reveals that breast cancer survivors have low levels of physical activity, suggesting the need of targeted interventions to enhance the physical activity behaviour of breast cancer survivors. Unfortunately, there is lack of data from the UK about the physical activity behaviours of women at various stages of diagnosis and treatment of breast cancer. Therefore, the aim of the present study was to assess physical activity levels in women at different stages of breast cancer pathway.

Methods: A convenient sample of patients was selected at various stages of presentation and treatment of breast cancer. Patients attending breast screening for NHSBSP (n=188), post-operative patients attending for chemotherapy (n=41) and breast cancer patients within one year's post-treatment (n=80) were invited to take part in this cross-sectional study.

Results: Based on the odds ratio, the likelihood of a chemotherapy participant not meeting physical activity guidelines (i.e., being in the low activity category) were three times higher than the odds of a NHSBPS attendee not meeting physical activity guidelines, and compared to post-treatment participants, the chemotherapy patient's odds of not meeting physical activity guidelines was four times higher. The odds of NHSBPS attendees being in the high activity category compared to the moderate category were three times higher than that of a post-treatment participant.

Conclusion: The current study suggests the need to establish robust physical activity interventions to enhance the physical activity behaviour of breast cancer survivors.

5.2.2 INTRODUCTION

Worldwide, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females (Jemal et al., 2011). In the UK, female breast cancer had the highest incidence rate of all cancers, with an average European age standardised rate of 124.2 cases per 100,000 population each year between 2007 and 2009 (ONS, 2012). As a large consequence of early detection and improved treatment strategies, UK breast cancer mortality rates are falling and in turn survival rates are improving (Nur et al., 2011) and thus there are now more breast cancer survivors than ever before. However, due to the chronic side-effects of breast cancer treatment, survivors may require diagnostic, therapeutic, supportive or palliative services many years post-diagnosis, which poses a major burden to already stretched healthcare resources. Therefore, interventions are required that can not only reduce the risk of developing breast cancer, but in addition, can benefit breast cancer survivors.

Lack of physical activity is a well-recognised risk factor in the development of breast cancer and evidence on the impact of physical activity on breast cancer survival is consolidating (World Cancer Research Fund/American Institute for Cancer Research, 2009). In prospective studies, an average 25% reduction in the risk of developing breast cancer was seen in the most physically active women compared to the least active women while this risk reduction is shown to be dose-dependent (Lynch et al., 2011).

Evidence also suggests that achieving recommended physical activity levels can improve disease-specific mortality after breast cancer diagnosis (Beasley et al., 2012). In addition, a recent Cochrane review demonstrated that physical activity can significantly improve the quality of life of breast cancer survivors (Mishra et al., 2012). However, despite these positive effects of physical activity, evidence reveals that breast cancer survivors have low levels of physical activity and many women decrease their physical activity following diagnosis (Irwin et al., 2003; Irwin et al., 2004). As such, targeting behaviours that may increase levels of physical activity may be beneficial for breast cancer patients. Unfortunately, there is a lack of data from the UK about the physical activity behaviours of women at various stages of diagnosis and treatment of breast cancer. Therefore, the aim of the present study was to assess physical activity levels in women at different stages of the breast cancer pathway, that is, during breast screening (i.e. pre-diagnosis of breast cancer), during chemotherapy and within one year post- breast cancer treatment.

5.2.3 METHODS

A convenience sample of patients at various stages of presentation and treatment of breast cancer was selected. Patients attending breast screening for NHSBSP (n=188), post-operative patients attending for chemotherapy (n=41) and breast cancer patients within one year's post-treatment (n=80) were invited to take part in this cross-sectional study. The chemotherapy patient group were recruited from breast clinics by the consultant breast surgeon and consultant oncologist to take part in an audit of physical activity. This required permission from the head of Research and Development at the hospital but not ethics approval.

Participants within each group completed an assessment which included demographics, physical activity questionnaires and anthropometric measurements. The height and mass of patients receiving chemotherapy and the patients within one-year post-treatment were measured directly in breast clinics at Russells Hall Hospital, Dudley. The assessment of the breast cancer screening attendees was carried out in a mobile screening unit located in Sandwell, West Midlands, and because mass and height could not be measured directly the self-reported height and mass were taken from these participants. Participant's height and mass were then used to calculate BMI. Each participant was facilitated to complete the validated long form International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003). The IPAQ assessed moderate and vigorous physical activity in four life domains: occupational, active transportation, domestic and leisure-time, and walking in the occupational, active transport and leisure-time domains. IPAQ was administered during face-to-face interviews by specifically trained researchers (Hallal et al., 2010).

Physical activity categories were classified based on IPAQ manual recommendations (http://www.ipaq.ki.se/scoring.pdf). Using MET-min·wk^{-1} as a means to combine aerobic activities of different types and intensities into a single measure of amount of activity, the IPAQ physical activity categories allow the categorisation of individuals into those who are meeting the current recommended physical activity guidelines (i.e. a ≥150 minutes of moderate-intensity physical activity per week) and those who are not (i.e. <150 min/week) (Bull and the Expert Working Groups, 2010). The IPAQ categorises physical activity into low (not achieving recommended levels), moderate and high activity categories. Based on

recent recommendations (Bauman et al., 2009), separate analysis were included using either moderate-to-high or high activity category alone to identify those meeting recommended physical activity guidelines

Statistical analysis

The physical activity data were explored to identify outliers. Outliers were identified by converting all scores to z-scores. Z-scores greater than 3.29 were classed as outliers. All outliers above this score were converted to one unit above the next highest score with a z-score below 3.29 (Tabachnik and Fidell, 1996). The distribution of all continuous outcomes, including body mass, BMI, IPAQ MET-min·wk^{-1} scores (work, active transport, domestic and leisure domain totals, walk, moderate, vigorous and overall physical activity) and IPAQ time variables (walk, moderate, vigorous, and overall physical activity time) were assessed. Distributions of these data were explored by first observing histograms and P-P plots for each variable. The z-score of skewness ($z_{skewness}$=skewness-0/$SE_{skewness}$) and kurtosis ($z_{kurtosis}$=skewness-0/$SE_{kurtosis}$) was then calculated for each variable, a z-score of greater than 1.96 was used to signify significant skewness and kurtosis, and therefore. If a variable's z-scores were lower than 1.96, that variable was deemed to be normally distributed. Data that was normally distributed were reported as mean (±*s*), while data not normally distributed were expressed as median (IQR). Height differences (only normally distributed variable) between groups were analysed with one-way Analysis of Variance (ANOVA) using Bonferoni post-hoc analysis for individual comparisons. Kruskal-Wallis tests were performed on all other variables of interest. These tests were analysed post hoc using the critical difference method as described by

Siegel and Castellan (1988). The level of significance was set at $p<0.05$ for between groups analysis.

Physical activity categorical data were expressed as number of participants and percentages, and were analysed via χ^2 analysis. We first compared the number of participants in the three physical activity categories between the three groups. If significant associations were found, we planned a number of comparisons to identify which comparisons were significant. There were nine planned comparisons, including the number of participants in the low activity category vs. moderate activity plus high activity category, number of participants in the high activity category vs. low activity plus moderate activity category, and the number of participants in the moderate activity vs. high activity category in the NHSBSP participants vs. the chemotherapy patients, the NHSBSP participants vs. the post-treatment patients, and the chemotherapy patients vs. the post-treatment patients. In order to counter the inflation of type I error caused by multiple comparisons, a Bonferoni correction was applied to the alpha level. In this case we planned nine comparisons, which gave us an alpha level of $p<0.0056$ (i.e. α 0.05/9=0.0056). Statistical analyses were performed using IBM® Statistical Package for Social Sciences® for windows version 20.0.

5.2.4 RESULTS

Characteristics of the participants in each group are presented in table 5.2.1. In brief, there was a slightly larger percentage (42%) of participants with a normal BMI (18-24.9 $kg \cdot m^2$) in the NHSBPS attendees compared to the chemotherapy and post-treatment group. All of the groups had a

similar majority of white British participants. There were less premenopausal women in the NHSBPS group compared to the other two groups. In addition, a larger percentage of the post-treatment group was current or previous smokers compared to the other two groups.

Table 5.2.1 Anthropometric, demographic and lifestyle characteristics of the participants

	NHSBPS (N=188)		**Chemotherapy (N=41)**		**Post-treatment (N=80)**	
	N	**%**	**N**	**%**	**N**	**%**
BMI ($kg \cdot m^2$)*						
o Obese (BMI= ≥ 30)	36	25	11	26	22	28
o Overweight (BMI=25-29.9)	46	32	9	22	29	36
o Normal (BMI=18-24.9)	60	42	13	31	28	35
o Underweight (BMI=<18)	0	0	0	0	1	1
o Missing	46	24	8	20	0	0
Ethnic Origin						
o White British	178	95	40	98	76	95
o Pakistani	1	0	1	2	0	0
o Indian	3	2	0	0	0	0
o Black Caribbean	2	1	0	0	2	3
o White Irish	2	1	0	0	1	1
o Other white background	1	1	0	0	1	1
o Chinese	1	1	0	0	0	0
o Missing	0	0	0	0	0	0
Menopausal status†						
o Premenopausal	13	7	10	24	16	20
o Perimenopausal	15	8	7	17	NR	NR
o Postmenopausal	146	78	24	59	64	80
o Unsure	8	4	0	0	0	0
o Missing	6	3	0	0	0	0
Employment status						
o Full-time	130 ‡	69	10	24	29	36
o Part-time	NR	NR	9	22	13	17
o Retired	48	25	8	20	21	26
o Unemployed	2	1	2	5	3	4
o Homemaker	1	1	4	10	8	10
o Other	0	0	0	0	3	4
o Missing	7	37	8	20	3	4
Smoking						
o Currently/previously	23	12	6	15	33	42
o No	165	88	35	85	47	48

Key: NR=not reported
* NHSBSP participants' BMI was computed from self-reported height and mass
† For post-treatment participants premenopausal status was determined as those participants who were currently or recently menstruating
‡ Figure represents those participants who were employed, both part-time and full-time, no separate figures were available for each

The descriptive statistics of the anthropometric and physical activity variables for each group are presented in table 5.2.2. There were no significant differences in height ($p=0.077$), body mass ($p=0.626$) or BMI ($p=0.854$) between the participant groups. Kruskal-Wallis tests revealed significant differences in overall ($p<0.01$) (Figure 5.2.1), domestic ($p<0.01$), leisure ($p<0.01$), moderate ($p<0.01$) and vigorous ($p<0.05$) physical activity (MET-min·wk^{-1}), and overall ($p<0.05$), moderate ($p<0.01$) and vigorous ($p<0.05$) physical activity time (min) between groups.

Post-hoc analysis revealed significantly lower overall ($p<0.001$), domestic ($p<0.001$), leisure ($p<0.001$) and moderate ($p<0.001$) physical activity (MET-min·wk^{-1}) and overall ($p<0.01$) and moderate ($p<0.001$) physical activity time (min) in the breast cancer patients undergoing chemotherapy compared to the NHSBSP participant group. The chemotherapy participants also performed significantly less overall ($p<0.001$), domestic ($p<0.001$), leisure ($p<0.001$), moderate ($p<0.05$) and vigorous ($p<0.01$) physical activity (MET-min·wk^{-1}) and overall ($p<0.01$), moderate ($p<0.01$) and vigorous ($p<0.05$) physical activity time (min) than the post-treatment participant group. The post-treatment breast cancer survivors performed significantly less overall, domestic ($p<0.05$) physical activity (MET-min·wk^{-1}) and moderate ($p<0.05$) physical activity time (min) than the NHSBSP participants.

Table 5.2.2 Mean ± *s* or median (interquartile range) for anthropometric measures and physical activity (PA) variables for NHSBPS participants, breast cancer patients undergoing chemotherapy, and breast cancer patients within one-year post-treatment (PA in MET-min·wk^{-1} unless stated otherwise)

	NHSBSP		Chemotherapy		Post-treatment			
Variable	**N**	**Median (IQR)**	**N**	**Median (IQR)**	**N**	**Median (IQR)**	**F/H statistic**	**p-value**
Height (m) mean ± *s*	179	1.63 ± 0.06	34	1.63 ± 0.07	80	1.61 (0.07)	3.494	0.077
Body mass (kg)	145	68.9 (19.6)	34	70.0 (21.6)	80	67.7 (14.2)	0.937	0.626
BMI (kg·m^2)	143	26.4 (7.3)	34	27.5 (5.3)	80	26.0 (6.1)	0.315	0.854
Overall PA	188	1689 (2345)*	41	933 (2127)†	80	1463 (1501)‡	12.286	0.002
Work PA	188	0 (0)	41	0 (0)	80	0 (0)	0.329	0.848
Active transport PA	188	66 (387)	41	50 (479)	80	132 (264)	1.133	0.567
Domestic PA	188	774 (1281)*	41	297 (897)†	80	541 (987)‡	14.52	0.001
Leisure PA	188	330 (1031)*	41	0 (314)†	80	350 (693)	11.253	0.004
Walk	188	396 (974)	41	297 (693)	80	396 (565)	0.838	0.658
Moderate PA	188	965 (1612)*	41	396 (1370)†	80	693 (1060)	17.642	0.000
Vigorous PA	188	0 (0)	41	0 (0)†	80	0 (0)	6.059	0.048
Overall PA time (min)	188	420 (571)*	41	270 (602)†	80	416 (390)	7.366	0.025
Walk time (min)	188	120 (295)	41	90 (210)	80	120 (171)	0.838	0.658
Moderate PA time (min)	188	235 (300)*	41	120 (385)†	80	178 (297)‡	11.679	0.003
Vigorous PA time(min)	188	0 (0)	41	0 (0)†	80	0 (0)	5.992	0.049

Key: * Significantly higher in the NHSBPS group vs. the chemotherapy group;
† Significantly lower in the chemotherapy group vs. the post-treatment group;
‡ Significantly lower than in the post-treatment group vs. the NHSBSP group.

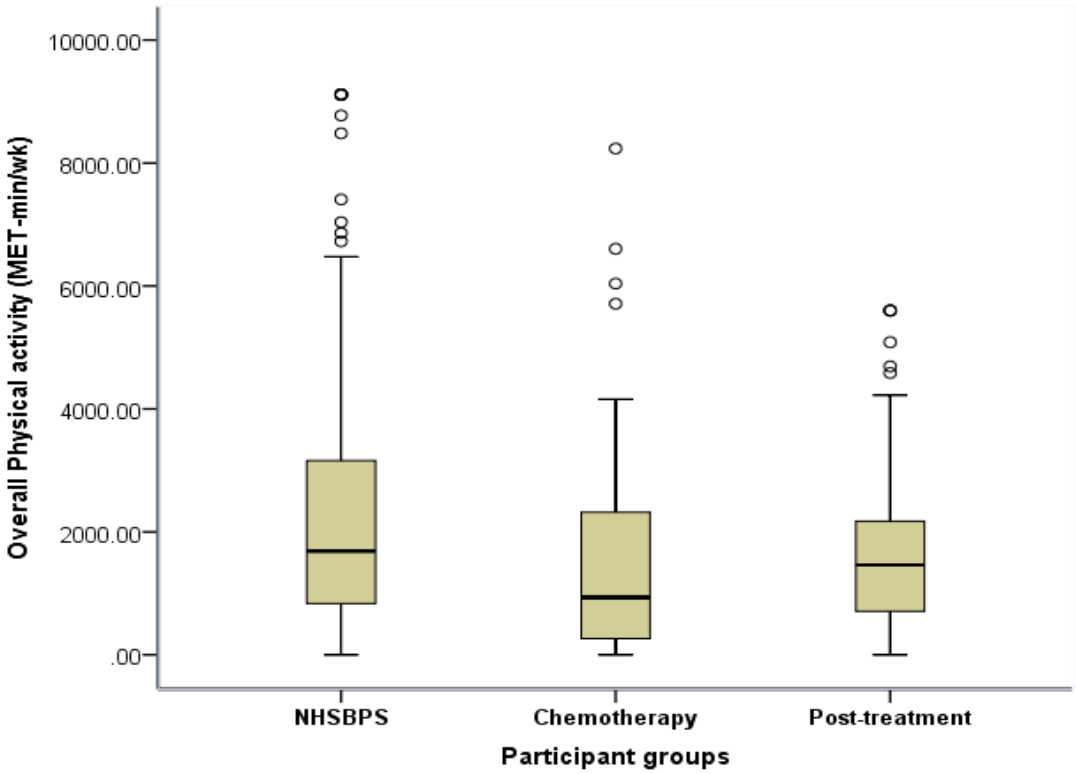


Figure 5.2.1 Box-plots (showing minimum value, 1st quartile, median, 3rd quartile and maximum values excluding outliers) for overall physical activity (MET-min·wk^{-1}) of NHSBPS attendees, chemotherapy breast cancer patients and post-treatment breast cancer survivors (circles above each boxplot represent values that are 1.5 IQRs above the 3rd quartile)

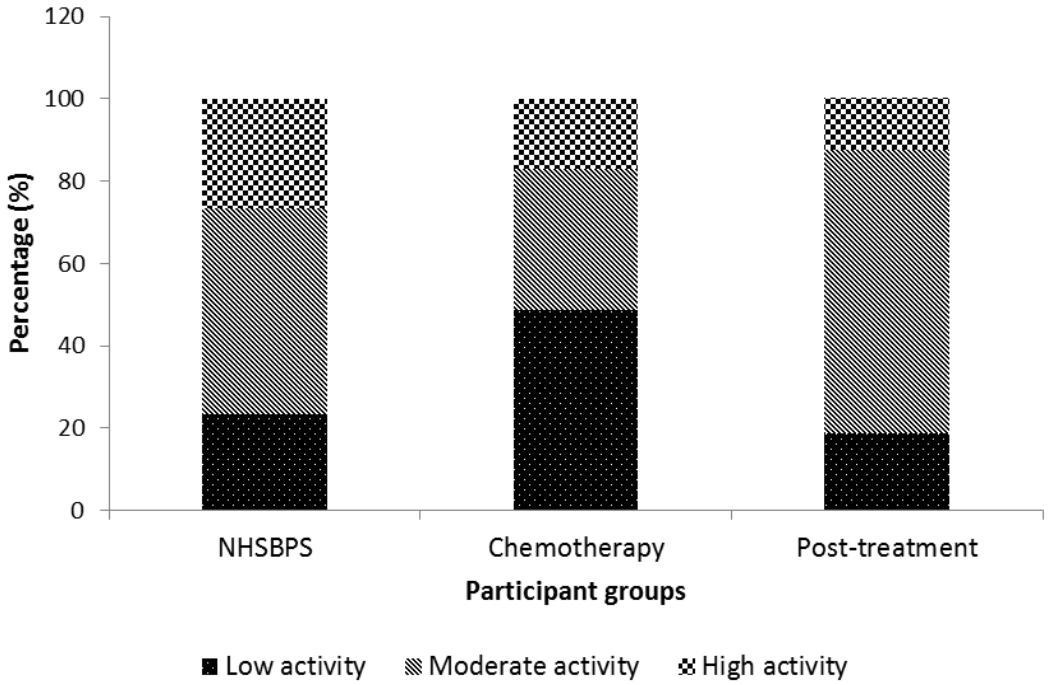


Figure 5.2.2 Percentage of participants in each physical activity category in the NHSBPS attendees, chemotherapy breast cancer patients and post-treatment breast cancer survivors

According to IPAQ physical activity categories, there was a higher proportion of participants (20 out of 41) categorised as low activity in the chemotherapy participant group compared to the NHSBSP group (44/188) and the post-treatment group (15/80) (Figure 5.2.2). A greater proportion of participants in the NHSBPS participant group were in the high activity category (50/188) compared to the chemotherapy and post-treatment groups (7/41 and 10/80, respectively), while a larger proportion of the post-treatment group were categorised as moderate activity (55/80) compared to the NHSBSP and chemotherapy groups (14/41 and 94/188, respectively).

There was a significant association between the population groups and the categories of activity χ^2 (4) =22.887, p<0.001. Post-hoc analysis with a Bonferoni correction applied (p<0.0056) revealed that chemotherapy patients were more likely to be categorised as low activity (i.e. not meeting recommended physical activity guidelines) than moderate or high category compared to the NHSBSP attendees (p=0.001) and post-treatment breast cancer patients (p=0.001), while post-treatment patients were less likely to be categorised in the high category than the moderate category compared to the NHSBPS participants (p=0.004). When we categorised those only in the high category as meeting recommended physical activity guidelines we found no association between participant groups.

Based on the odds ratio, the odds of a chemotherapy participant not meeting physical activity guidelines (i.e. being in the low activity category) were 3.1 times higher than the odds of a NHSBPS attendee not meeting physical activity guidelines, and compared to post-treatment participants,

the chemotherapy patient's odds of not meeting physical activity guidelines was 4.1 times higher. The odds of NHSBPS attendees being in the high activity category compared to the moderate category were 2.9 times higher than that of a post-treatment participant.

5.2.5 DISCUSSION

Results revealed that women receiving chemotherapy for breast cancer performed significantly lower physical activity in a number of IPAQ domains compared to the women attending NHS breast screening, and breast cancer patients who were within one year post-treatment. The post-treatment breast cancer patients also performed significantly less physical activity compared to the breast screening participants. Chemotherapy patients were less likely to be meeting the recommended guidelines when compared to the other two groups.

The finding of relatively low levels of physical activity in the two breast cancer patient groups is supported by past research. Previous studies have reported low levels of physical activity in patients receiving chemotherapy (Clark et al., 2007; Demark-Wahnefried et al., 1997), and have ascribed this finding largely to the side-effects of treatment, and treatment-related fatigue in particular (Clark et al., 2007). In the US, Irwin and colleagues (2004) surveyed the self-reported physical activity levels of 806 breast cancer patients within three years post-diagnosis, and found that when household and gardening activities were excluded, only 32% of breast cancer survivors achieved recommended levels of physical activity. Similarly, in the current UK based study there were relatively few

participants in the post-treatment group who reported high moderate-to-vigorous activity (i.e. categorised as high activity).

Although, it was not possible to ascertain in this current study, previous studies comparing breast cancer patients pre-diagnosis physical activity levels to their post-diagnosis levels, have found decreases in physical activity from pre- to post-treatment (Irwin et al., 2003; Littman et al., 2010). In a prospective cohort study (Irwin et al., 2003) that compared the self-reported physical activity of 812 breast cancer patients, reported an 11% decrease in total physical activity (hours/week) from pre- to post-diagnosis in women treated for radiation and chemotherapy. Subsequent studies have also found a similar decrease in physical activity in the 12 months after diagnosis relative to before diagnosis (Littman et al., 2010). These observed decreases have been attributed to persistent negative side-effects of breast cancer treatment including fatigue, nausea, and pain (Hartvig et al., 2006; Schwartz, 2000). Consistent with the findings of the current UK study, the results of the above US-based studies suggest that pre-breast cancer diagnosis physical activity levels are higher than the physical activity levels of patients post-diagnosis.

However, while the general finding in the literature supports lower in physical activity in pre-diagnosis to during treatment to post-treatment breast cancer populations, a recent finding from a Swedish study suggests that this may not be true for all women (Johnsson et al., 2013). The authors (2013) observed that breast cancer patients who had been physically active before their cancer diagnosis and women who had received information about physical activity were more physically active

during chemotherapy. Therefore, further research is required to establish how pre-breast cancer diagnosis physical activity along with other possible factors can mediate the levels of physical activity post-treatment.

Our study has several limitations. As is the case with all cross-sectional studies, it was not possible to attribute a temporal relationship between the group treatment status (i.e. breast screening, chemotherapy and post-treatment) and physical activity. That is, although we have found an association between physical activity levels and the treatment status of the participants, there is no evidence that the treatment status of participants was the cause of the reported physical activity. Furthermore, the cross-sectional design of the current study provided a “snap shot” of physical activity behaviour within the three UK based study groups. Hence, it is possible that this “snap shot” of physical activity reported by the participants in each group were not representative of their usual levels of physical activity. Moreover, we assessed physical activity via the self-report IPAQ questionnaire, which requires participants to recall past activity, and is therefore, a subjective means of estimating individual physical activity levels that may be influenced by recall bias and social desirability bias. However, this design provides real-time information regarding the physical activity status of breast cancer populations, which can facilitate the design of pragmatic interventions that can be delivered within the NHS. A further limitation of our study is that we cannot be sure that these findings are generalizable to women attending breast screening and women who are receiving or have completed breast cancer treatment because our sample included only women from the Black Country area of the West Midlands in the UK. Our samples of chemotherapy and post-

treatment breast cancer patients were also relatively small, which further limits our ability to generalise. The NHSBSP sample was chosen as a “pre-diagnosis” comparison group based on their status as an “at risk of breast cancer” group. However, clearly not all of the patients sampled will develop breast cancer, and therefore, this group may not be representative of breast cancer patients pre-diagnosis. Finally, BMI for the group of screening attendees was self-reported. This may have influenced the data of the present study; however, the effects of physical activity on BMI and/or the effects of the different stages of breast cancer were not amongst the main aims of the present study.

5.2.6 CONCLUSIONS

In summary, we found that breast cancer patients receiving chemotherapy had lower levels of physical activity compared to women attending breast screening and breast cancer patients within one-year post-treatment, while post-treatment breast cancer survivors had lower levels of physical activity group compared to the breast screening group. The relatively low physical activity levels of the post-treatment breast cancer survivors means that a large proportion of this group were not sufficiently exposed to the potential benefits of physical activity on breast cancer survival. The findings of this current study, highlights the need to establish robust physical activity interventions to enhance the physical activity behaviour of post-treatment breast cancer survivors in the UK at a time when the negative effects of chemotherapy begin to resolve and patients are more receptive to interventions designed to enhance their physical activity levels.

5.3 A home-based physical activity intervention in breast cancer survivors; a randomised controlled trial

5.3.1 ABSTRACT

Introduction: Randomised controlled trials have demonstrated that adherence to supervised physical activity interventions may result in improved in health outcomes and HRQoL in breast cancer survivors. However, the findings of supervised facility-based physical activity interventions may not generalise to patients who have limited access to exercise facilities because of financial, transportation or time-related difficulties. Home-based physical activity interventions are potentially advantageous as they may mitigate many of the difficulties associated with facility-based physical activity interventions. Therefore, the purpose of this study was to investigate the effects of a home-based physical activity intervention on physical activity levels, anthropometric measures, HRQoL and blood biomarkers in post-adjuvant therapy breast cancer survivors.

Methods: Eighty post-adjuvant therapy breast cancer survivors (age=53.6±9.4y; height=161.2±6.8cm; mass=68.7±10.5kg) were randomly allocated to a six-month home-based physical activity intervention or a usual care group. End points included changes in self-reported physical activity levels assessed via the IPAQ, mass, BMI, body fat %, HRQoL measured by the FACT-B questionnaire and fasting insulin, glucose, insulin resistance (HOMA), TC, HDL-C, LDL-C and TG between baseline and 6-months. The intervention group received an intervention aimed at encouraging the achievement of current recommended physical activity guidelines of 150 $min \cdot wk^{-1}$ of moderate physical activity. The intervention consisted of a face-to-face physical activity consultation during the first visit, followed by support telephone calls at the end of months one, two

and three, and a physical activity reminder postcard during the last two months. Ethical approval was obtained from the Black Country NHS Research Ethics Committee (West Midlands, UK). Pre-post intervention differences were analysed using linear mixed model analysis.

Results: Self-reported total and moderate physical activity significantly increased from baseline to post-intervention in the intervention compared to usual care (mean difference, MD=580 MET-min·wk^{-1}, *P*=0.04, *d*=0.48 and MD=112 MET-min·wk^{-1}, *P*<0.01, *d*=0.57, respectively). Both body mass and BMI decreased significantly from baseline to post-intervention in the intervention compared to usual care (MD, -1.6 kg, *P*=0.03, and MD, -0.6 kg·m^2, *P*=0.02, respectively). There was no significant change in body fat % scores (*P*=0.16). Of the HRQoL variables only the trial outcome index and breast cancer subscale improved significantly in the physical activity group compared to the usual care group (MD=5.2, *P*=0.016, *d*=0.55 and MD=2.9, *P*=0.002, d=0.71, respectively). Of the blood biomarkers only TC and LDL-C was significantly reduced in the physical activity group compared to the usual care group (MD, -0.45 units, *P*=0.006, and -0.308 units, *P*=0.046, respectively).

Conclusion: We found that a home-based physical activity intervention resulted in significant improvements in self-reported physical activity, mass and BMI, breast cancer specific HRQoL and TC and LDL-C. The portability, feasibility and relatively low cost of this current intervention makes it a promising intervention that could benefit a large number of breast cancer survivors, therefore, it will be important to assess whether modifications would be needed when employed in older and perhaps less motivated breast cancer survivors.

5.3.2 INTRODUCTION

Worldwide, breast cancer is the most frequently diagnosed cancer and a leading cause of cancer death among females (Jemal et al., 2011). In the UK, female breast cancer had the highest incidence rate of all cancers, with an average rate of 124.2 cases per 100,000 population (European age-standardised) each year between 2007 and 2009 (ONS, 2012). In 2006, there were 296,037 (790.8 per 100,000) UK women diagnosed and living with breast cancer within a ten-year period. Furthermore, the number of women with breast cancer has been predicted to increase in the future, with recent projections estimating a 44% increase in breast cancer incidence in England from 2001 figures by 2020 (Moller et al., 2007).

As a large consequence of early detection and improved treatment strategies, UK breast cancer mortality rates are falling and in turn survival rates are improving (Nur et al., 2011). As a result there are now more breast cancer survivors than ever before. Breast cancer survivors may experience side-effects of treatment years after diagnosis, such as fatigue, pain, cognitive dysfunction, neuropathy, sexual problems, cardiotoxicity and reduced quality of life (Azim et al., 2011; Bovelli et al., 2010; van Dalen et al., 2010). In addition, breast cancer survivors are at an increased risk of weight gain, obesity, recurrence, new primary cancer, CVD and diabetes (Azim et al., 2011; Bovelli et al., 2010). Therefore, breast cancer survivors may require diagnostic, therapeutic, supportive or palliative services many years post-diagnosis which poses a major challenge to already stretched healthcare services. Accordingly, simple, effective and inexpensive interventions for breast cancer survivors that

can reduce the side-effects of treatment, improve the health and quality of life and possibly reduce the risk of early mortality are needed.

Encouraging breast cancer survivors to adopt a healthy lifestyle post-treatment may be important for improving health and quality of life of survivors and in turn reduce the healthcare burden (Demark-Wahnefried et al., 2005). In particular, higher levels of physical activity, may reduce breast cancer-related and all-cause mortality (Schmidt et al., 2013; Cadmus Bertram et al., 2011; Chen et al., 2011; Irwin et al., 2011; Friedenreich et al., 2009; Holmes et al., 2005). However, physical activity levels are generally low among breast cancer survivors and many women decrease their physical activity following diagnosis (Irwin et al., 2003; Irwin et al., 2004). Therefore, interventions are required to improve the physical activity levels of breast cancer survivors post-diagnosis.

RCTs have found beneficial effects of physical activity, including improvements in cardiorespiratory fitness, enhanced quality of life, reduced fatigue and lower weight gain compared to control groups (Cadmus et al., 2009; Rogers et al., 2009; Payne et al., 2008; Daley et al., 2007; Matthews et al., 2007; Herrero et al., 2006; Pinto et al., 2005; Courneya et al., 2003). However, most physical activity intervention trials consist of either entirely or partly facility-based interventions, and therefore, the findings of these trials may not generalise to patients who have limited access to exercise facilities because of transportation or time-related difficulties. To overcome this problem some trials have provided entirely home-based physical activity interventions (Musanti et al., 2012; DeNysschen et al., 2011; Rogers et al., 2009; Payne et al., 2008; Heim et

al., 2007; Matthews et al., 2007; Vallance et al., 2007; Pinto et al., 2005). In addition to mitigating transport and time-related difficulties, home-based interventions are also advantageous because they are less expensive than supervised, facility-based interventions and do not require participants to attend classes or maintain a health club membership to sustain physical activity.

Trials employing home-based interventions appear to show good adherence to physical activity programmes and significant increases in physical activity in intervention patients compared to controls (Rogers et al., 2009; Matthews et al., 2007; Vallance et al., 2007; Pinto et al., 2005). As reported in the systematic review and meta-analysis of interventions (section 2.8), these trials have found positive effects on cardiorespiratory fitness, physical condition domain of self-esteem, quality of life, fatigue and sleep when comparing intervention groups to controls. However, all of the above studies were either based in North America or Germany (Heim et al., 2007), therefore, there is currently no data regarding the effectiveness of home-based physical activity interventions in UK breast cancer survivor populations. As a consequence it is unclear how generalisable the findings of these trials are to breast cancer survivors in the UK.

Few studies have given consideration to the long-term implications of individuals' adherence and motivation to exercise. Most of the trials investigating the effects of physical activity in breast cancer survivors have not included a physical activity counselling component designed to promote physical activity behaviour change within the physical activity

interventions. Without the support to change beyond what is provided by the exercise facilities or the physical activity programmes provided, it is unlikely breast cancer survivors will be able to maintain their participation once the specified intervention period lapses (Daley et al., 2004). Only three home-based intervention trials consisted of a physical activity specific counselling component, which included either both face-to-face counselling and support telephone calls (Rogers et al., 2009; Matthews et al., 2007) or support telephone calls alone (Pinto et al., 2005). Although the findings of these home-based physical activity trials are promising, there were a number of limitations which limit the generalizability of the results. Matthew and colleagues (2007) involved a small sample of postmenopausal breast cancer survivors (n=36), Rogers et al. (2009) consisted of a relatively small (n=41) number of sedentary breast cancer survivors receiving hormone therapy, while the sample in Pinto et al. (2005) consisted of a number of patients diagnosed with less severe, non-invasive stage 0 breast cancer (16%) and none diagnosed with stage III breast cancer, and a large proportion of highly educated and affluent patients (40% of patients with a bachelor's degree or graduate degree and 61% of patients with a household income of more than $50,000). In addition, all of these trials were relatively short in duration (12 weeks) and based in the USA. Hence, trials with a larger sample size and longer duration that examine the effect of home-based physical activity interventions with an additional counselling component in a more representational sample of UK breast cancer survivors are required.

Therefore, the aim of this current study was to investigate whether post-adjuvant therapy breast cancer survivors can adopt a relatively

inexpensive home-based physical activity programme and determine the effects of adherence to such a programme on physical activity levels, weight gain, HRQoL, insulin resistance and blood lipid profiles. The main hypothesis was that breast cancer survivors who received the home-based physical activity intervention would have increased self-reported total physical activity from baseline to post-intervention compared to the usual care participants. We also hypothesised that breast cancer survivors in the intervention group would have higher HRQoL, better weight maintenance, lowered insulin resistance and improved blood lipid profiles, when compared with usual care participants post-intervention.

5.3.3 METHODS

Trial design

This current study was a two-armed, parallel design RCT that compared a six month home-based physical activity intervention to usual care. Individualised face-to-face consultations and telephone counselling to individualise goal-setting and assess progress formed the key components of this programme. The present study reports data collected at baseline and six months. Recruitment of participants took place between January 2010 and March 2013.

One hundred and fifty female breast cancer patients who had completed adjuvant therapy were invited to take part in the current trial. Of these women, 53% (n=80) were found to fully meet the study criteria, were interested in participating and were willing to be randomised to a treatment or usual-care control group. Seventy breast cancer patients were excluded due to reasons including not meeting eligibility criteria, not wanting to

participate in exercise or have blood taken, and felt they did not need exercise advice. Six of the 70 patients were excluded because they did not attend the initial assessment, and these patients could not be contacted to establish the reasons for their non-attendance.

Participants

Women attending breast cancer clinics at Russells Hall Hospital (The Dudley Group of Hospitals, NHS Foundation Trust, UK), were invited to enrol on the study by cancer care nurses working within these clinics. Interested patients were given a study information booklet and were contacted by the primary researcher via telephone a week later. Participants were eligible to take part in the current study if they 1) were female, 2) were aged less than 69 y, 3) were diagnosed with invasive breast cancer (Stage I-III) within two years of enrolment, 4) were post-surgery and had no surgery planned for the next six months at least, 5) had fully completed adjuvant therapy (radiotherapy and/or chemotherapy) not including hormonal therapy, 6) were willing to be randomised 7) and willing to maintain contact with the investigators over the six months. Exclusion criteria included 1) the inability to participate in physical activity because of severe disability (e.g., severe arthritic conditions), 2) psychiatric illness and 3) vulnerable subjects, such as pregnant women or any other patient where physical activity was not approved by their oncologist. The study was reviewed, approved and monitored by the investigational review boards of the Russells Hall Hospital and all participants provided written consent prior to data collection.

Volunteers were asked to visit the testing venue (Research and Development Unit, Russells Hall Hospital, Dudley) early in the morning following a 12 hour overnight fast. Participants were asked not to change their normal physical activity patterns from when the appointment was arranged to the day of the appointment. All participants were subjected to the same data collection procedures overseen by the same investigator. Upon arrival, participants' height, mass and body composition were assessed. Participants were then asked to complete a demographics questionnaire, which included questions relating to ethnicity, time since diagnosis and end of treatment, co-morbidities and medical history, family history of breast cancer and reproductive and menstrual history.

Home-based physical activity Intervention

Following consent and randomisation, breast cancer patients in the intervention group received an intervention (Figure 5.3.1) aimed at encouraging the adoption of a more physically active lifestyle. Participants received a face-to-face consultation, followed by a support telephone call at the end of months one, two and three. During the last two months (4 and 5) patients received physical activity reminder leaflets encouraging their participation in home-based physical activity. The intervention was based on the findings from previous research (Rogers et al., 2008; Jones and Courneya, 2002), which found that breast cancer survivors had strong preferences for the receipt of face-to-face counselling from exercise professionals that were associated with a cancer centre, either at the cancer centre or at home. Both of the above studies (2008; 2002) also found clear preferences for walking, moderate-intensity activity and for exercising at home or outdoors. This current study has been developed

based on the preferences of breast cancer survivors, and therefore, may be a promising model for delivering physical activity promotion programmes for these individuals.

Months of the Intervention	0	1	2	3	4	5	6
Initial assessment and face-to-face consultation	√						
Support telephone call		√	√	√			
Mailed physical activity prompts					√	√	
Post-intervention assessment							√

Figure 5.3.1 Plan of the Six Month Home Based Physical Activity Intervention

The face-to face consultation was conducted by the primary researcher within the Research and Development unit of Russells Hall Hospital immediately after the initial baseline measurements were taken. To ensure consistency in intervention delivery across sessions and participants, a semi-structured motivational interviewing-based intervention protocol was developed to guide intervention delivery. The topics covered in the consultation were similar to other trials that incorporated a physical activity counselling component (Rogers et al., 2009; Matthews et al., 2007; Pinto et al., 2005). These topics included current physical activity behaviour (e.g. activities the participants enjoyed and felt they could do on a regular basis, ways of fitting physical activity into daily life and previous experiences of physical activity), decision balance exercise (e.g. possible gains and losses that might occur with increased physical activity levels), benefits of physical activity in general and specific to breast cancer survivors, perceived barriers (e.g. greatest barriers to being more active

and suggestions on how to overcome these), prompts to seek social support (e.g. family, friends, workmates and others who might encourage exercise, someone to talk to while doing physical activity to provide encouragement), goal setting (e.g. participants own goals, goals of intervention and determination of short term goals), types and intensities of physical activity (e.g. explanation of light, moderate and vigorous intensity physical activity with examples specific to participants, such as, taking a brisk walk so that you are mildly breathless but can still hold a conversation), safety advice (e.g. walking/cycling in dark, ensuring they could be seen and someone knows where they're going, avoid busy/dangerous roads etc.) and basic lifestyle information (e.g. basic dietary information, portion size, fat intake, smoking and hydration in generally and during activity) (see Appendix S).

During the face-to-face consultation, the four core motivational interviewing principles, namely, expressing empathy, developing discrepancy, rolling with resistance and supporting self-efficacy, were applied (Rosengren, 2009; Miller and Rollnick, 1991). Motivational interviewing can be defined as a person-centred method of guiding to elicit and strengthen personal motivation for change (Resnicow and McMaster, 2012). This approach aims to assist individuals to work through their ambivalence or resistance about behaviour change. Specific therapeutic techniques, including open-ended questions, affirmation, reframing, reflective listening, importance and confidence rulers, values-sort exercises and summarising, that are in line with motivational interviewing principles were used as needed. The consultations lasted approximately 30 to 45 minutes. Patients were given a physical activity pack consisting of

an interactive information booklet and a DVD (previously developed by Breast Cancer Care) that provided further information of topics such as exercising safety, exercise intensity, dealing with fatigue and exercising with lymphedema. Patients who did not have access to a DVD were encouraged to watch it with a friend or family member. Information about local physical activity opportunities were also provided, including an exercise initiative run by Dudley Council in local parks.

To facilitate behaviour change over the longer term, the participants were contacted by the primary researcher by telephone one, two and three months after randomisation. The focus of these calls was to prevent relapse back to sedentary behaviour and/or improve maintenance of a physically active lifestyle, and covered topics similar to the face-to-face consultation such as enhancing motivation, goal setting, self-efficacy for activity, overcoming barriers, providing positive reinforcement and developing appropriate activity plans for home-based physical activity. Calls lasted approximately 15 to 20 minutes, were guided by standardised phone call scripts and as with the face-to-face counselling session the principles of motivational interviewing were applied. Participants were encouraged to telephone the research team should they encounter any problems or relapse in their efforts to increase their physical activity. Participants were also sent physical activity reminder leaflets that encouraged participation in regular physical activity at the end of the fourth and fifth months of the intervention (see Appendix T).

The intervention was developed to promote enjoyment, motivation, confidence and compliance, as well as minimising the possibility of injuries

and discomfort. The initial goal of the intervention (months 1-3) was for participants to progress towards accumulating 30 minutes of moderate intensity exercise on three to five days per week. During months 3 to 6, the intervention participants were encouraged to work towards accumulating at least 30 minutes of moderate-intensity physical activity on five to seven days per week in broad agreement with current public health guidelines (Bull and the Expert Working Groups, 2010). If participants were already achieving this on trial entry they were, as a minimum, actively encouraged to maintain their level of physical activity. Participants were encouraged to first focus on the frequency of their physical activity and then duration. Physical activity in the form of walking was particularly encouraged. The impact due to walking is low and strain on the feet and joints is minimised. Moreover, it does not require any specialized equipment. However, we did not preclude and encouraged participants to perform other activities that they enjoyed. Participants were advised to refrain from activity if they felt unwell. They were told to immediately contact their doctor (GP) and notify the research site if they had problems breathing, developed chest pain, felt faint or dizzy, developed a joint problem, developed high blood pressure or became pregnant. In these circumstances, the clinician (consultant surgeon) of the research team made a clinical decision as to whether the patient should refrain from physical activity temporarily or withdraw from the intervention.

Usual Care Group

Since not informing patients about the benefits of physical activity may be considered unethical, participants randomised to the usual care arm received standard information regarding physical activity (i.e. the current

recommended physical activity guidelines), as provided to all breast cancer patients treated at the site. Participants completed the same baseline and post-six month intervention assessments as the physical activity intervention group.

Outcomes

After randomisation, participants completed the International Physical Activity Questionnaire (IPAQ) followed by the Functional Assessment of Cancer Therapy-Breast (FACT-B) HRQoL questionnaire. Questionnaires were administered in this order to all participants and questionnaire completion was facilitated by the same trained researcher via a face-to-face interview, in order to minimise participant bias. The primary outcome of the current study was total physical activity (MET-min·wk^{-1}). Secondary outcomes included body mass, body mass index (BMI) body fat percentage (%), all other IPAQ physical activity, FACT-B variables and total cholesterol (TC), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), triglycerides (TG), blood glucose and insulin concentrations and insulin resistance via HOMA. All assessments were made at baseline and within two weeks of completing the six-month intervention. The details of assessments are described in chapter 4.3.

Sample size calculation

Power calculations were based on total physical activity as the primary outcome. A similar trial (Matthews et al., 2007) reported that the mean difference from baseline to 12 weeks follow-up using self-reported physical activity was 16.5 MET-h·wk^{-1} greater in the intervention group compared to the usual care group. Power calculations were carried out using the

equation below (Equation 5.1) (Noordzij et al., 2010). With at least 36 participants in each group (N=72), the trial would have 80% power at p<0.05. To allow for 10% attrition we aimed to recruit 80 participants (40 in each group).

Equation 5.1 Sample size calculation

$$n = \frac{2 \times [(a+b)^2] \times \sigma^2}{(\mu_1 - \mu_2)^2}$$

Where, n=sample size in each group, a=normal deviate for different significance levels (Type I error or alpha) for two tailed alternative hypothesis (i.e. 1.96), b=normal deviate for different power, probability of rejecting null hypothesis when it is not true or one minus probability of type II error (i.e. 0.842), σ^2=population variance (i.e. combined *s* for the intervention and control groups), μ_1=population mean in intervention group, μ_2=population mean in control/comparison group.

Randomisation

Randomisation of participants in this current study was conducted via the Cancer Research UK Clinical Trials Unit of the University of Birmingham. A computer generated random numbers list was used to allocate all participants into intervention groups and allocate 40% of participants in each group into a substudy. The substudy consisted of a separate exercise tolerance test and blood pressure assessment carried out on a separate day to the outcomes outline above. The findings from the substudy will be presented in section 5.4. The random allocation sequence was kept concealed from the primary researcher. Patients were allocated

to intervention and usual care groups on a 1:1 allocation ratio. The patients were stratified into the two groups (intervention and usual care) after taking into consideration adjuvant chemotherapy. This stratification can add to the credibility of a trial, as it ensures treatment balance, allowing easy interpretation of outcomes without adjustment (Beller et al., 2002). The results of randomisation were explained to the participants after they completed the demographics questionnaire. The primary researcher who carried out both the initial and post-intervention assessments was not blinded to the assignment of participants to intervention groups.

Statistical analysis

Only data from breast cancer survivors who had attended their initial assessments were included in the analysis. All data was inputted onto to a Microsoft Excel™ spreadsheet (Microsoft Corporation) and transferred to Statistical Package for Social Sciences (SPSS) (IBM™) for windows version 20.0 for analysis. For all analyses, we employed the intention-to-treat (ITT) approach (Newell et al., 1992).

Physical activity data outliers were identified by converting all scores to z-scores. Z-scores greater than 3.29 were classed as outliers. All outliers above this score were converted to one unit smaller than the next highest score with a z-score below 3.29 (Tabachnik and Fidell, 2007). The distribution of all continuous, baseline and post-intervention outcomes were assessed. Distributions of these data were explored by first observing histograms and P-P plots for each variable. The z-score of skewness ($z_{skewness}$=skewness-0/$SE_{skewness}$) and kurtosis ($z_{kurtosis}$=

skewness-0/$SE_{kurtosis}$) was then calculated for each variable, a z-score of greater than 1.96 was used to signify significant skewness and kurtosis, and thus, data not normally distributed. Of all variables, only total cholesterol, HDL-C and LDL-C were normally distributed at both baseline and post-intervention. Normally distributed variables were expressed as mean±*s*, while all other variables were described using medians and interquartile ranges (IQR). Categorical data were presented as number of participants and percentages.

To correct for non-normal distributions, variables not normally distributed were log transformed. Anthropometric data and blood biomarkers (TG, glucose, insulin and HOMA) were positively skewed, and were therefore, log transformed to base 10, log10(X). Because the physical activity data contained zero values, they were transformed to log10(X+1). FACT variables data were negatively skewed, and therefore, were first reverse log transformed (highest score+1–X) and then log10(X) transformed. Repeated-measures linear mixed model analysis was performed on all continuous trial outcomes to assess differences in group changes from baseline to post-intervention (i.e. 6-months from baseline). Linear mixed models use all available data and provide a valid analysis when data are missing at random (Diggle et al., 2002). Time (baseline and post-intervention) was selected as the repeated effects variable. Treatment group alone was considered as fixed effects and participants as the random factor.

For each outcome variable, we tested a model with a scaled identity structure for a random effect and an autoregressive [AR(1)] structure for

the repeated effect versus a model that had a compound symmetry structure for the random effect and an unstructured matrix for the repeated effect. To compare the adequacy of smaller models versus more complex models the likelihood ratio (LLR) test was used. The null hypothesis of this test states that the smaller model provides as good a fit for the data as the larger model. If the null hypothesis was rejected, then the alternative, larger model was chosen as this would provide significant improvement over the smaller model. The LLR test statistic was computed by subtracting the Maximum Log Likelihood (MLE) of the larger model from the MLE of the smaller model. Degrees of freedom were then computed by subtracting the total number of parameters in the smaller model from the total parameters in the larger model. The significance of the test statistic was established by comparing it to critical values for the chi-square statistic with the computed degrees of freedom. If the test statistic was greater than the critical values for a chi-square statistic (i.e. $\geq \chi^2$ value for 0.05) with the computed degrees of freedom then the difference between models is significant. That is, the new model (unstructured variance) presented a significant improvement over the original AR(1) model. A non-significant difference between models meant the null-hypothesis could be accepted and the simpler model could be chosen. In all cases there was no significant improvement in models, therefore, the less complex, AR(1) covariance structure results were presented. Results of the linear mixed model analysis on log transformed data are presented in tables 5.3.5, 5.3.6 and 5.3.7. We also provide the mean difference, standard error and 95% confidence intervals (CI) of the untransformed data to aid clinical interpretation.

Chi-square analysis was performed on categorical IPAQ data. The breast cancer subscale score (BCS), FACT-General, FACT-Breast and trial outcome index (TOI) FACT HRQoL variables were categorised based on whether participants experienced a minimum clinically important increase in these variables from baseline to post-intervention. These minimum important clinically improvements were categorised based on a previous study, which suggested minimum clinically important increases of two points for the BCS, seven points for the FACT-B total score and five points for the FACT-G and the TOI scores (Eton et al., 2004). Chi-square analysis was then performed to examine intervention and usual care groups for differences in the number of participants who experienced a minimum important clinically increase in these variables. Statistical tests and corresponding p values were two-sided; a p value of less than 0.05 was reported as statistically significant. Cohen's d effect sizes for linear mixed model analysis was calculated based on the estimate comparing baseline values of the intervention group to the 6-month values in the intervention group and the baseline and 6-month values for the usual care group. Effect sizes for the t-values of each comparison were calculated by converting the t value to d using the formula below:

Equation 5.1 Conversion of t values to effect sizes (Cohen's-d) (Rosenthal and Rosnow, 1991)

$$d = t(n_1 + n_2)/\left(\sqrt{df} \times \sqrt{(n_1 \times n_2)}\right)$$

According to Cohen (1992) a small effect would be denoted as d=0.2, medium effect d=0.5 and large effect d=0.8. For the purposes of this

report, effect sizes of <0.20 were interpreted as small, 0.2 to <0.5 as small to moderate, 0.5 to <0.8 as moderate to large, and ≥0.8 as large.

5.3.4 RESULTS

Flow of participants through the trial and recruitment

Eighty participants were recruited for this trial between January 2010 and March 2013. Flow of participants through the study is provided in Figure 5.3.2. Participants were randomised to either the intervention or usual care group (40 participants in both groups). Seventy participants completed the trial, with 37 and 33 completers in the intervention group and usual care group, respectively. Of the three participants assigned to the intervention group, one participant dropped out of the trial due to a recurrence of breast cancer, while another participant cited sciatica as the reason for dropping out, and the third participant discontinued the trial due to unspecified personal reasons. Two of the participants in the usual care group dropped out of the trial because they did not want to attend the hospital for re-assessment, another patient dropped out due to a hip operation, and four participants could not be contacted to arrange re-assessment and therefore, did not give reasons for dropping out.

Participant characteristics at baseline

Table 5.3.1 provides the baseline characteristics overall and by group assignment. Baseline data was collected from 80 breast cancer survivors (age=53.6±9.4 y; height=161±6.8 cm; mass=68.7±10.5 kg) who have completed the six month study duration. Both the intervention group (age=52.4±10.3 y; height=162±6.2 cm; mass=70.9±11.8 kg) and the usual care group (age=54.7±8.3 y; height =160±7 cm; mass=68.2±11.2 kg)

consisted of 40 participants. The number of patients who had undergone chemotherapy was 42 (52.5%). The same number of patients completed chemotherapy in the intervention as the usual care group (n=21; 52.5%). Patients had received their breast cancer diagnosis an average of 38±20.8 weeks before their initial assessment. The mean number of weeks since the patients completed treatment (i.e. surgery/radiotherapy/chemotherapy) was 10.5±9.0 weeks for the 80 patients.

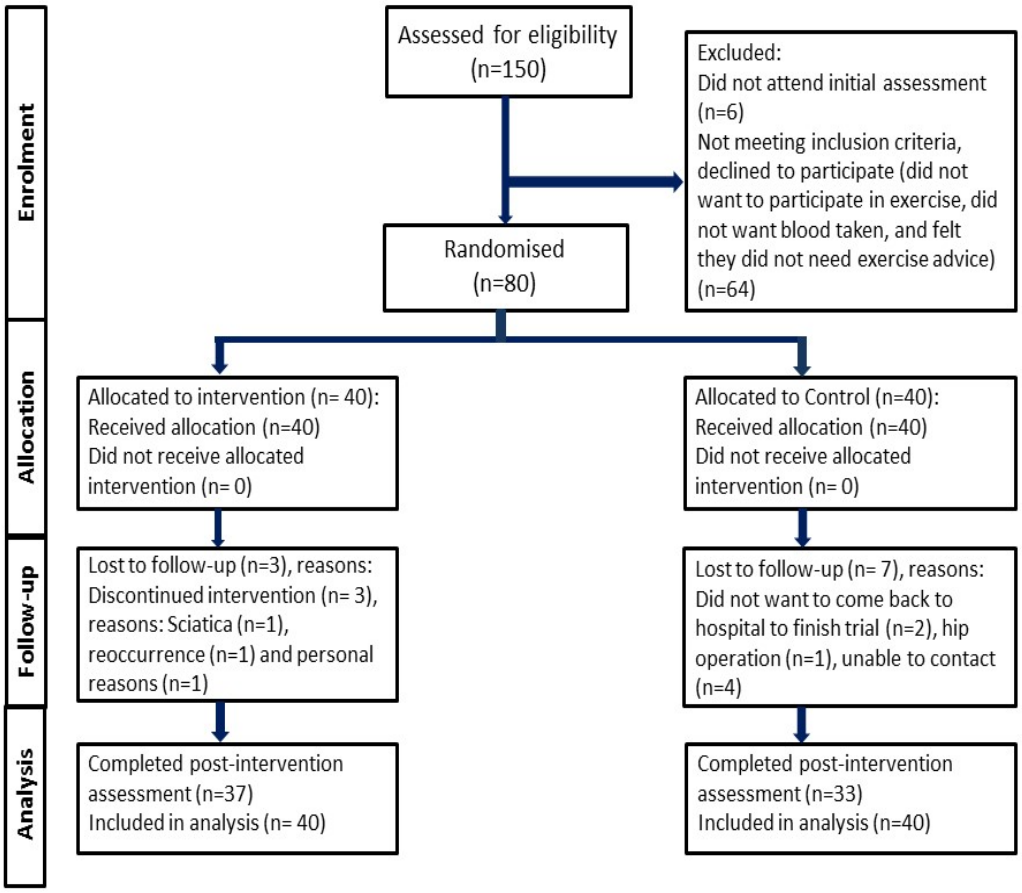


Figure 5.3.2 Flow of participants through the trial

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Table 5.3.1 Personal characteristics of the participants at baseline (intervention, n=40; usual care, n=40)

	No. participants (%) overall	**No. participants (%) intervention**	**No. participants (%) usual care**
Mean±*s* age (y)	53.6±9.4	52.4±10.3	54.7±8.3
Mean±*s* time since diagnosis (wk)	38.0±20.8	42.2±20.0	34.4±21.1
Mean±*s* time since end of treatment (wk)	10.5±9.0	8.9±7.3	12.0±10.3
Ethnic Origin:			
• White British	76 (95)	38 (95)	38 (95)
• White Irish	1 (1)	0 (0)	1 (3)
• Other white background	1 (1)	1 (3)	0 (0)
• Black Caribbean	2 (3)	1 (3)	1 (3)
BMI ($kg \cdot m^2$):			
• Obese (BMI=≥ 30)	22 (28)	12 (30)	10 (25)
• Overweight (BMI=25-29.9)	29 (36)	13 (33)	16 (40)
• Normal (BMI=18-24.9)	28 (35)	15 (38)	13 (33)
• Underweight (BMI=< 18)	1 (1)	0 (0)	1 (3)
Family History of breast cancer:			
• Yes	15 (19)	8 (20)	7 (18)
• No	65 (81)	32 (80)	33 (83)
Smoking:			
• Current	5 (6)	0 (0)	5 (13)
• Previously	28 (35)	12 (30)	16 (40)
• Never	47 (59)	28 (70)	19 (48)
• Mean±*s* cigarettes/day	4.3±7.2	3.0±5.4	5.7±8.5
• Mean±*s* years smoking	8.3±13.5	6.1±11.5	10.5±15.0
Alcohol drinkers:			
• Yes	57 (71)	28 (70)	29 (72)
• No	23 (29)	12 (30)	11 (28)
Mean±*s* no. of days/week when alcohol is drank	1.8±1.6	1.8±1.7	1.8±1.6
Mean±*s* no. glasses on days when drinking most	1.7±1.5	1.8±1.6	1.7±1.5
Drink type :			
• Wine	43 (75)	23 (82)	20 (69)
• Beer	7 (12.5)	2 (7)	5 (17)
• Spirits	7 (12.5)	3 (11)	4 (14)
Current or previous co-morbidities:			
• Diabetes	3 (4)	2 (5)	1 (3)
• Hypertension	12 (15)	4 (10)	8 (20)
• High Cholesterol	6 (8)	3 (8)	3 (8)
• Heart disease	4 (5)	2 (5)	2 (5)
• Vascular disease	2 (3)	1 (3)	1 (3)
• Asthma or chronic bronchitis	9 (11)	3 (8)	6 (15)
• Osteoarthritis	13 (16)	4 (10)	9 (23)
• Rheumatoid arthritis	3 (4)	2 (5)	1 (3)
• Kidney disease	2 (3)	0 (0)	2 (5)
• Liver disease	1 (1)	0 (0)	1 (3)

	No. participants (%) overall	No. participants (%) intervention	No. participants (%) usual care
Parity:			
• Nulliparous	11 (14)	4 (10)	7 (18)
• Parous	69 (86)	36 (90)	33 (82)
Number of children:			
• 1-2	60 (75)	32 (80)	28 (70)
• 3	7 (9)	3 (8)	4 (10)
• 4	2 (3)	1 (3)	1 (3)
Mean±*s* age at birth of 1st child (y):	26.8±4.9	27.2±4.8	26.4±5.0
Breast fed children:			
• Yes	45 (56)	23 (58)	22 (55)
• No	35 (44)	17 (42)	18 (45)
Currently menstruating:			
• Yes	16 (20)	8 (23)	8 (20)
• No	64 (80)	31 (78)	32 (80)
Oral Contraceptive use (current/previous):			
• Yes	64 (80)	30 (75)	34 (85)
• No	16 (20)	10 (25)	6 (15)
• Mean±*s* years taken	9.2±7.8	10.0±7.9	8.5±7.7
HRT:			
• Never	59 (74)	31 (78)	28 (70)
• Previously/Currently	21 (26)	9 (22)	12 (30)
• Mean±*s* years taking HRT	6.9±4.9	5.9±3.8	7.6±5.5
Marital Status:			
• Single	3 (4)	2 (5)	1 (3)
• Married	59 (74)	32 (80)	27 (68)
• Not married, living with partner	5 (6)	3 (8)	2 (5)
• Not married, not living with partner	1 (1)	1 (3)	0 (0)
• Divorced or separated	9 (11)	1 (3)	8 (20)
• Widowed	3 (4)	1 (3)	2 (5)
Highest qualification:			
• O-levels or GCSE	35 (44)	15 (38)	20 (50)
• A-level or equivalent	5 (6)	3 (8)	2 (5)
• NVQ	1 (13)	3 (8)	7 (18)
• College degree or diploma	16 (20)	10 (25)	6 (15)
• Bachelor degree	6 (8)	5 (13)	1 (3)
• Post-graduate degree	1 (2)	0 (0)	1 (3)
• Other or not listed	6 (8)	4 (10)	2 (5)
• Mean±*s* school leaving age	17.0±4.0	17.8±4.7	16.3±3.0
Employment status:			
• Employed full-time	13 (17)	5 (13)	8 (20)
• Employed part-time	29 (36)	16 (40)	13 (33)
• Homemaker	8 (10)	4 (10)	4 (10)
• Unemployed	3 (4)	0 (0)	3 (8)
• Unable to work due to illness	3 (4)	3 (8)	0 (0)
• Retired	21 (26)	11 (28)	10 (25)
• Missing	3 (4)	1 (3)	2 (5)

The baseline characteristics of participants in the intervention and usual care groups were similar in terms of age, BMI, presence of family history of breast cancer, alcohol drinking behaviour, number of children, age at first birth, numbers who had breastfed, numbers still menstruating, oral contraceptive pill use, HRT use, education and employment status (see table 5.3.1). There were a greater number of participants in the usual care group who reported co-morbidities (hypertension, asthma and osteoarthritis), nulliparity and being divorced or separated compared to the intervention group.

The anthropometric characteristics of participants in the intervention group were similar to that of participants in the usual care group (see table 5.3.2). However, those in the usual care group were more active compared to the intervention group at baseline (see table 5.3.2). The difference in median physical activity time was almost 160 min between the intervention and usual care group. However, most of the additional activity of the usual care group can be attributed to a greater amount of domestic physical activity in this group. Regarding IPAQ physical activity categories, 19% (n=15/80) of the participants were classified as low activity, while 69% (n=55/80) and 13% (n=10/80) were categorised as moderate and high activity, respectively, at baseline. In the intervention group, 20% (n=8/40), 75% (n=30/40) and 5% (n=2/40) of participants were categorised as low, moderate and high activity, respectively, while in the usual care group 5% (n=2/40), 75% (n=30/40) and 13% (n=5/40) of participants were categorised as low, moderate and high activity, respectively, at baseline. Therefore, at baseline 15% (n=6) more participants were categorised in the low activity category in the

intervention group compared to the usual care group. There were no evident differences in HRQoL variables or blood biomarkers between groups at baseline (see Tables 5.3.3 and 5.3.4, respectively). Twenty nine participants were characterised as dyslipidaemic at baseline, based on increased concentrations of TC (>6.2 mmol·L^{-1}), 22 had increased TG (>1.7 mmol·L^{-1}), 21 had increased LDL-C (>4.13 mmol·L^{-1}) and two had decreased levels of HDL-C (<1.03 mmol·L^{-1}). The number of participants characterised as dyslipidaemic were similar across groups (data not shown). Twenty-nine participants (intervention, n=14; usual care, n=15) had undetectable insulin concentrations (i.e. insulin <14.0 pmol·L^{-1}). Ten participants, five in each group, were characterised as insulin resistant (i.e. HOMA ≥2.5).

Physical activity outcomes

Self-reported total physical activity (both MET-min·wk^{-1} and time variables) significantly increased from baseline to post-intervention in the intervention group compared to usual care group (mean difference, 580 MET-min·wk^{-1}; p=0.04, and mean difference, 169 min; p=0.03, respectively). In particular, moderate physical activity (both MET-min·wk^{-1} and time variables) and domestic physical activity increased in the intervention group compared to the usual care group over the intervention period (p=0.004 and 0.04, respectively). No significant differences were found for any of the other physical activity variables (see Table 5.3.5).

Chi-square analysis was not possible on physical activity categorical data because greater than 20% of the expected counts were less than five and some of the expected frequencies were below one. Collapsing the

moderate and low categories into one category did not remedy this. Therefore, the physical activity data are presented as frequencies in those who completed post-intervention assessments. Post-intervention, only 5% (n=2/37) of the intervention group participants were categorised as low activity compared to 10% (n=4/33) in the usual care group. The majority of the intervention group (75%, n=30/37) and 50% (n=20/33) of the usual care were categorised as moderate activity, while 13% and 23% were categorised as high activity in the intervention and usual care groups, respectively. Of the participants in the intervention group categorised as low activity at baseline, 88% (n=7/8) and 12% (n=1/8) moved to the moderate and high activity category, respectively, post-intervention. While in the usual care group, 50% (n=2/4) remained in the low activity category while one participant each moved from low to moderate and low to high activity categories, post-intervention. Of the intervention participants categorised as moderate activity at baseline, 85% (n=23/27), 7.5% (n=2/27) and 7.5% (n=2/27) did not change, increased to the high activity category or decreased from the moderate to low category, respectively. While, 80% (n=16/22) 18% (n=4/22) and 9% (n=2/22) of usual care participants categorised as moderate activity at baseline, did not change, increased to the high activity category or decreased from the moderate to low category, respectively. The two participants in the intervention group who were categorised as high activity remained in the high category post-intervention, however, 43% (n=3/7) of the usual care participants categorised as high activity dropped down to the moderate category and 57% (n=4/7) remained in the high category post-intervention.

Table 5.3.2 Median (IQR) for anthropometric and physical activity (PA) variables at baseline for all participants and for intervention and usual care groups at baseline and post-intervention (6-months) (all physical activity data reported as MET-min·wk^{-1} unless stated otherwise)

Variables	All	Intervention		Usual Care	
	Baseline (N=80)	Baseline (N=40)	6-mo (N=37)	Baseline (N=40)	6-mo (N=33)
Body mass (kg)	67.7 (14.2)	67.3 (15.8)	66.9 (17.7)	68.5 (12.3)	67.3 (6.3)
BMI (kg·m^2)	26.0 (6.1)	26.0 (6.3)	25.1 (7.2)	26.0 (5.8)	26.0 (4.9)
Body fat (%)	35.3 (7.3)	35.1 (8.3)	35.3 (8.6)	35.3 (6.9)	36.6 (6.2)
Total PA	1463 (1276)	998 (1390)	1746 (1291)	1617 (1394)	1802 (1450)
Work PA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Active transport PA	132 (264)	140 (223)	198 (157)	83 (446)	198 (380)
Domestic PA	541 (987)	396 (1043)	462 (1056)	636 (892)	657 (651)
Leisure PA	350 (693)	350 (594)	706 (1056)	367 (842)	594 (833)
Walk-cycle-leisure PA*	572 (979)	501 (502)	1072 (1077)	627 (502)	792 (887)
Walk	396 (565)	338 (437)	594 (462)	479 (780)	578 (660)
Moderate PA	693 (1059)	396 (1062)	660 (1040)	792 (890)	918 (1258)
Vigorous PA	0 (0)	0 (0)	0 (320)	0 (0)	0 (0)
Total PA time (min)	441 (389)	300 (377)	455 (353)	459 (401)	440 (296)
Walk time (min)	120 (172)	103 (133)	170 (223)	145 (236)	175 (200)
Moderate PA time (min)	178 (297)	120 (298)	152 (315)	207 (252)	197 (196)
Vigorous PA time (min)	0 (0)	0 (0)	0 (40)	0 (0)	0 (5)

* Computed by summing occupational walking, active transport (walking and cycling) and leisure physical activity (MET-min·wk^{-1})

Table 5.3.3 Median (IQR) HRQoL (FACT-B) variables at baseline for all participants and for intervention and usual care groups at baseline and post-intervention (6-months)

	All	Intervention		Usual Care	
	Baseline (N=80)	Baseline (N=40)	6-mo (N=37)	Baseline (N=40)	6-mo (N=33)
Physical well-being (PWB) (0-28)	24 (7)	24 (8)	26 (5)	24 (7)	26 (5)
Social well-being (SWB) (0-28)	25 (4)	26 (3)	24 (6)	24 (6)	26 (5)
Emotional well-being (EWB) (0-24)	21 (6)	21 (7)	22 (4)	21 (5)	21 (5)
Functional well-being (FWB) (0-28)	23 (6)	23 (8)	23 (6)	24 (7)	24 (8)
Breast cancer subscale (BCS) (0-36)	24 (9)	24 (7)	27 (10)	28 (9)	25 (10)
FACT-General (FACT-G) (0-108)	92 (21)	92 (23)	93 (19)	92 (17)	95 (22)
FACT-Breast (FACT-B) (0-144)	116 (26)	116 (30)	118 (28)	117 (23)	119 (30)
Trial Outcome Index (TOI) (0-92)	72 (21)	71 (21)	75 (19)	73 (16)	76 (21)

Key: FACT-G=PWB+SWB+EWB+FWB; FACT-B=FACT-G + BCS; TOI=PWB+FWB+BCS
Higher scores represent better quality of life

Table 5.3.4 Mean±*s* and median (IQR) blood biomarkers at baseline for all participants and for intervention and usual care groups at baseline and post-intervention (6-months)

	All	Intervention		Usual Care	
	Baseline (N=80)	Baseline (N=40)	6-mo (N=37)	Baseline (N=40)	6-mo (N=33)
Total cholesterol	5.77±1.17	5.75±1.30	5.42±1.09	5.79±1.04	5.93±0.91
High-density lipoprotein	1.62±0.32	1.65±0.30	1.62±0.33	1.58±0.34	1.60±0.30
Low-density lipoprotein	3.50±1.00	3.44±1.15	3.18±1.01	3.56±0.84	3.64±0.84
Triglycerides	1.25 (0.93)	1.20 (1.05)	1.20 (0.78)	1.30 (1.75)	1.4 (0.78)
Glucose	4.80 (0.70)	4.85 (0.68)	4.7 (0.88)	4.70 (0.98)	4.8 (0.58)
Insulin	31.5 (34.4)	29.5 (32.9)	30.0 (33.4)	33.0 (35.9)	21.5 (27.9)
Insulin resistance*	1.39 (1.10)	1.30 (1.10)	1.45 (1.45)	1.5 (1.40)	1.2 (1.13)

* Measured via HOMA
Units of measurement: Total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides and glucose in $mmol \cdot L^{-1}$, insulin in $pmol \cdot L^{-1}$

Table 5.3.5 Linear mixed model results of log transformed data and delta values (6-months minus baseline) of untransformed data for anthropometric and physical activity (PA) variables comparing intervention group to usual care group at baseline to post-intervention (6-months) (6-months) (all physical activity data reported as MET-min·wk^{-1} unless stated otherwise)

	Log Transformed Data*					Untransformed data†		
	Difference estimate	**SE difference**	**95% CI**	**p-value‡**	**Effect size (*d*)**	**Mean difference**	**SE difference**	**95% CI**
Body mass (kg)	-0.010	0.004	-0.019 to -0.001	**0.026**	0.51	-1.61	0.79	-3.18 to -0.04
BMI (kg·m^2)	-0.010	0.005	-0.019 to -0.001	**0.023**	0.50	-0.62	0.30	-1.22 to -0.01
Body fat (%)	0.006	0.008	-0.021 to 0.010	0.495	0.16	0.36	0.65	-0.94 to 1.66
Total PA	0.234	0.110	0.139 to 0.454	**0.037**	0.48	579.77	281.54	17.96 to 1141.58
Work PA	0.027	0.197	-0.365 to 0.419	0.892	0.03	-45.85	44.95	-135.54 to 43.85
Active transport PA	-0.185	0.303	-0.789 to 0.419	0.544	0.14	23.16	62.65	-101.86 to 148.18
Domestic PA	0.477	0.233	0.014 to 0.940	**0.044**	0.46	152.41	209.81	-266.26 to 571.08
Leisure PA	0.255	0.308	-0.358 to 0.868	0.410	0.19	382.46	153.49	76.19 to 688.74
Walk-cycle-leisure PA	0.120	0.213	-0.304 to 0.544	0.575	0.13	436.28	166.39	104.26 to 768.30
Walk	0.176	0.256	-0.335 to 0.687	0.494	0.16	172.94	124.90	-76.30 to 422.18
Moderate PA	0.518	0.205	0.109 to 0.928	**0.014**	0.57	111.87	235.22	-357.5 to 581.25
Vigorous PA	0.313	0.305	-0.293 to 0.919	0.307	0.23	265.17	106.79	52.08 to 478.26
Total PA (min)	0.224	0.098	0.0289 to 0.418	**0.025**	0.52	168.81	69.78	29.57 to 308.06
Walk (min)	0.161	0.211	-0.260 to 0.582	0.449	0.17	52.47	37.84	-23.04 to 127.97
Moderate PA (min)	0.502	0.169	0.165 to 0.839	**0.004**	0.67	114.41	64.41	-14.11 to 242.94
Vigorous PA (min)	0.107	0.179	-0.250 to 0.464	0.553	0.13	17.04	8.76	-0.43 to 34.51

* Anthropometric data were log transformed to base 10, log10(X), while all physical activity data were transformed to log10(X+1)

† Delta descriptive statistics were only available for the 37 participants in the intervention and the 33 participants in the usual care who had both baseline and post-intervention values

‡ Significant results in bold

Table 5.3.6 Linear mixed model results of log transformed data and delta values (6-months minus baseline) of untransformed data for HRQoL FACT-B variables comparing intervention group to usual care group at baseline to post-intervention

	Log Transformed Data*					Untransformed data†		
	Difference estimate	**SE difference**	**95% CI**	**p-value‡**	**Effect size (*d*)**	**Mean difference**	**SE difference**	**95% CI**
Physical well-being	0.002	0.070	-0.137 to 0.141	0.977	0.01	0.68	2.01	-3.34 to 4.69
Social well-being	-0.058	0.080	-0.216 to 0.101	0.471	0.16	-0.72	0.70	-2.11 to 0.67
Emotional well-being	0.011	0.066	-0.121 to 0.142	0.873	0.04	-0.27	0.55	-1.37 to 0.82
Functional well-being	0.037	0.066	-0.094 to 0.167	0.581	0.13	1.90	0.93	0.06 to 3.75
Breast cancer subscale	0.169	0.053	0.062 to 0.275	**0.002**	0.71	2.91	1.11	0.70 to 5.11
FACT-General	0.155	0.074	-0.119 to 0.177	0.695	0.09	2.68	3.74	-4.77 to 10.15
FACT-Breast	0.112	0.068	-0.023 to 0.246	0.103	0.37	5.42	2.76	-0.09 to 10.94
Trial Outcome Index (TOI)	0.146	0.059	0.027 to 0.264	**0.016**	0.55	5.23	2.30	0.64 to 9.82

* FACT variables data were first reverse log transformed (highest score+1–X) and then log transformed base 10, log10(X)
† Delta descriptive statistics were only available for the 37 participants in the intervention and the 33 participants in the usual care who had both baseline and post-intervention values
‡ Significant results in bold
Higher scores represent better quality of life

Table 5.3.7 Linear mixed model results of log transformed data and delta values (6-months minus baseline) of untransformed data for blood biomarker variables comparing intervention group to usual care group at baseline to post-intervention

	Mean Difference†	SE difference	95% CI	p-value‡	Effect size (*d*)
Total cholesterol	-0.447	0.156	-0.136 to -0.760	**0.006**	0.65
High-density lipoprotein	0.138	0.159	-0.178 to 0.455	0.378	0.20
TC/HDL ratio*	-1.27	0.066	-0.121 to 0.142	0.873	0.46
Low-density lipoprotein	-0.308	0.151	-0.006 to -0.610	**0.046**	0.46
Triglycerides*	0.102	0.100	-0.098 to 0.302	0.242	0.27
Glucose*	0.079	0.185	-0.291 to 0.449	0.626	0.11
Insulin*	-7.511	11.322	-30.061 to 15.039	0.333	0.22
Insulin resistance*	-0.459	0.628	-1.716 to 0.798	0.096	0.38

* Variables log transformed base 10, log10(X), untransformed descriptive statistics are presented with p-values and *d* of log-transformed comparisons

† Delta descriptive statistics were only available for the 37 participants in the intervention and the 33 participants in the usual care who had both baseline and post-intervention values

‡ Significant results in bold

Anthropometric outcomes

Both body mass and BMI decreased significantly from baseline to post-intervention in the intervention group compared to usual care group (mean difference, -1.6 kg; p=0.03, and mean difference, -0.6 $kg \cdot m^2$; p=0.02, respectively). There was no significant change in body fat % scores (p=0.16) (see Table 5.3.5).

HRQoL outcomes

Analyses highlighted a significant moderate to large improvement in TOI scores in the physical activity group compared to the usual care group over the 6-month intervention period (mean difference, 5.2 units; p=0.016). A significant moderate to large improvement for BCS scores was also recorded for the physical activity group compared to the usual care group over the study period (mean difference, 2.9; p=0.002). No significant differences between physical activity and usual care groups for PWB (p=0.98), SWB (p=0.47), EWB (p=0.87), FWB (p=0.58), FACT-G (p=0.70) and FACT-B (p=0.10) were recorded (Table 5.3.6).

Chi-square analysis of the BCS, FACT-G, FACT-B and TOI variables revealed significant associations between intervention and usual care groups and the number of participants who experienced minimum clinically important increases in BCS, χ^2 (1)=6.19, p=0.013, and TOI , χ^2 (1)=8.34, p=0.004. Significantly more participants in the intervention group experienced minimum clinically important improvements in BSC and TOI between baseline and post-intervention compared to the usual care group (n=21/37 vs. n=9/33 or 57% vs. 27%; and n=24/37 vs. n=10/33, or 65% vs. 30%). No significant associations were found between intervention and

usual care groups and the number of participants who experienced minimum clinically important changes in FACT-G, χ^2 (1)=0.31, p=0.63, and FACT-B, χ^2 (1)=1.67, p=0.23, variables.

Blood biomarker outcomes

We found significant reductions TC and LDL-C in the physical activity group compared to the usual care group over the 6-month intervention period (mean difference, 0.45 units; p=0.006) -0.308 0.151 -0.006 to -0.610 0.046 0.46. However, no significant changes were observed in TG, HDL-C, glucose, insulin or HOMA between the groups over the intervention period (see Table 5.3.7).

5.3.5 DISCUSSION

As hypothesised, breast cancer survivors who received the home-based physical activity intervention significantly increased our primary outcome, self-reported total physical activity (MET-min·wk^{-1} and time) when compared with usual care post-intervention. We also found further significant improvements in body mass, BMI, domestic (MET-min·wk^{-1}) and moderate (both MET-min·wk^{-1} and time) physical activity, HRQoL (BCS and TOI) and TC and LDL-C concentrations in the intervention compared to usual care. All of the significant improvements above were found to have moderate to large effect sizes, apart from the small to moderate effect observed for domestic physical activity. Significantly more participants in the intervention group experienced minimum clinically important improvements in BSC (increases of ≥2 points) and TOI (increases of ≥5 points) between baseline and post-intervention compared to the usual care group. However, we observed no significant

improvements in body fat, and other physical activity, HRQoL and blood biomarker variables.

Our findings of increases in total and moderate physical activity are consistent with previous home-based physical activity interventions with an additional physical activity counselling element (Rogers et al., 2009; Matthews et al., 2007; Pinto et al., 2005). Two previous similar trials (Matthews et al., 2007; Pinto et al., 2005) found improvements in self-reported physical activity in the intervention groups compared to usual care, while another study (Rogers et al., 2009) found increases in objective physical activity but not self-reported physical activity. Unlike one of the previous studies (Matthews et al., 2007), we found no significant increases in self-reported walking from baseline to post-intervention in the intervention group compared to the usual care group. However, while in the current study we encouraged walking as an effective way of meeting recommended physical activity guidelines, we also encouraged other moderate activities, such as other aerobic exercise (e.g. running, stationary cycling, elliptical trainers, rowing machines, swimming, etc.) and the use of fitness DVD's. In addition, the IPAQ assesses walking in occupational and active transport domains as well as leisure domains, so it is also probable that the usual care engaged in this type of activity as much as intervention participants as part of general daily activities.

Unlike similar previous studies, we found significant reductions in body mass and BMI (Rogers et al., 2009; Matthews et al., 2007; Pinto et al., 2005). Although the mean pre-post differences in the intervention compared to usual care could be considered modest for both outcomes (-

1.6 kg and -0.6 $m \cdot kg^{-1}$), it does represent at the least more effective weight management. The significant reductions in mass and BMI were surprising given that the intervention did not focus on weight loss and did not involve any calorie restriction. However, previous research (Pate et al., 1996) has found positive associations between physical activity and healthy eating behaviours; therefore, it is possible that participants in the intervention group changed to healthier eating behaviours when becoming more physical activity, which in turn may have had a beneficial effect on mass and BMI. The reasons for our significant improvements compared to the lack of improvements seen in earlier studies (Rogers et al., 2009; Matthews et al., 2007; Pinto et al., 2005) could be due in part to the longer duration of the current study compared to the earlier studies (6-months vs. 12-weeks). However, we found no significant improvements in body fat % despite the improvements in mass and BMI. It is possible that the method of assessing body fat %, bioelectrical impedance, was not a precise enough method to measure small changes in body fat over time (Dehghan and Merchant, 2008).

The findings of significant increases in the HRQoL variables, BCS and TOI, indicate that our intervention may have specific benefits for breast cancer survivors given that higher BCS scores indicates fewer breast cancer-specific symptoms, and higher TOI scores indicates greater physical and functional well-being and fewer breast cancer-specific symptoms. One previous study (Courneya et al., 2003) investigated the effects of a physical activity intervention on HRQoL in breast cancer survivors, and found similar significant improvements in the TOI and BCS scores (mean difference=6.3 and 3.6, respectively; both $p<0.001$). Only

one of the previous home-based physical activity interventions with an additional physical activity counselling element measured HRQoL (Rogers et al., 2009). Using the same FACT questionnaire, the authors (2009) reported significantly greater improvements social well-being in the intervention group versus usual care group, but no significant improvements were found in the other HRQoL variables. Unfortunately, the TOI was not calculated for this study (Rogers et al., 2009) so it was not possible to make a comparison with this current study. Significant improvements in the FACT-B variable in the intervention group versus usual care group was reported by an earlier home-based physical activity trial involving breast cancer survivors, which did not have a counselling component (Vallance et al., 2007). The authors (2007) only reported the FACT-B variable.

The reasons for the differences in HRQoL between previous studies are unclear. However, it is likely that the breast cancer stage, treatment received and both the time since diagnosis and the end of treatment may influence participant's responses to the items with the FACT questionnaire. For instance, given that our sample was on average 38 weeks post-treatment, it is possible that items such as "I have nausea" may no longer be relevant. Nevertheless, we did find minimum clinical significant improvements in BSC and TOI in the intervention versus usual care, which can be interpreted in part as fewer reported breast cancer-specific symptoms such as "shortness of breath", "change in weight" and "effect of stress on illness" in the intervention group compared to the usual care group over the six month study period.

The significant reductions observed in TC and LDL-C as a result of home-based physical activity were encouraging given that the recent findings of Santos et al. (2014) suggesting that LDL-C promotes breast cancer cell proliferation, migration and loss of adhesion, which are hallmarks epithelial to mesenchymal transition. In addition, existing literature investigating the prevention of CVD emphasize the role of TC and LDL-C with a supplementary role for HDL-C and a modest role for TG (ECS and EAS, 2011; O'Keefe et al., 2004; Edwards and Moore, 2003). Every 1.0 $mmol \cdot L^{-1}$ reduction in TC and LDL-C has been associated with a corresponding 50% and 22% reduction in CVD mortality and morbidity, respectively (CTTC, 2010; Stamler et al., 1993). Extrapolating from the available data, the observed 0.33 $mmol \cdot L^{-1}$ and 0.26 $mmol \cdot L^{-1}$ mean reductions in TC and LDL-C, respectively, in the intervention group in the current study, would equate to CVD mortality risk reductions of 16.5% and 5.72%. Evidence supports our finding of the role that physical activity can play in favourably altering lipid profiles. In a recent meta-analysis, aerobic exercise was found to result in significant mean reductions in TC and LDL-C, a small but significant mean increase in HDL-C and unaltered TG concentrations (Pattyn et al., 2013). Previous studies involving breast cancer survivors have also observed favourable effects of physical activity on lipid profiles. Fairey and colleagues (2005) found significant reductions in TG and non-statistically significant but clinically important changes in TC, HDL-C and LDL-C after an aerobic exercise intervention compared to usual care. Similarly, two other studies employing combined aerobic exercise and resistance training interventions in breast cancer survivors found favourable effects of lipid profiles. Mefferd and co-workers (2007) observed reductions in TC to a level no longer at risk for CVD and

significant changes in the ratio of TC to HDL-C and TG concentrations, while Nuri et al. (2012) found significant increases in HDL-C and reductions in TG.

Hyperinsulinemia may play a role in facilitating breast cancer recurrence and progression (Goodwin et al., 2002b). Insulin may have a mitogenic effect on breast cells, inhibit sex hormone binding globulin and promote the release of adipokines, leptin, TNF-α and IL-6, which stimulate aromatase activity, angiogenesis, proliferation, invasion and metastasis and inhibits apoptosis (Lann and LeRoth, 2008; Rose et al., 2004; Kaaks, 1996). However, we found no significant changes in glucose, insulin and insulin-resistance, which was consistent with several previous studies involving physical activity interventions in breast cancer survivors and non-diabetic participants (Pattyn et al., 2013; Schmitz et al., 2005; Fairey et al., 2003). Conversely, other physical activity interventions in breast cancer survivors found significant reductions in insulin (Nuri et al., 2012; Irwin et al., 2009; Ligibel et al., 2008) and glucose (Nuri et al., 2012). However, only one of these studies involved an aerobic exercise only intervention (Irwin et al., 2009), the other studies consisted of aerobic exercise and resistance training combined (Nuri et al., 2012; Ligibel et al., 2008). Therefore, the effect of aerobic exercise on glucose-insulin dynamics is unclear due to a lack of agreement between available studies (Fairey et al., 2003; Irwin et al., 2009). There are perhaps alternative reasons for the lack of reductions in glucose, insulin and insulin-resistance in the current study, including an insufficient sample size to detect differences between groups, an insufficient reduction in body fat (Ross et al., 2004) and the fact that the majority of participants did not have diabetes (Pattyn et al., 2013).

In order to interpret the findings of this current study, the strengths and limitations must be carefully considered. The strengths of the current study include its randomised design, the use of an independent clinical trials unit to randomise patients and conceal the allocation sequence from the principle investigator and an analysis plan that adhered to intention-to-treat principles. We reported moderate to large effect sizes for all but two of our statistically significant findings. We recruited participants over two full calendar years; therefore, it is unlikely that our results were influenced by the seasonal changes in physical activity suspected in previous research (Vallance et al., 2007). The generalisability of our findings is increased by the recruitment of breast cancer survivors diagnosed with stage I to III rather than only early-stage breast cancer and the fact that we included both pre- and post-menopausal breast cancer survivors. The results of the trial were promising given that the intervention was relatively brief, inexpensive and highly feasible given that it was home-based and consisted of a single in-person counselling session followed by three support telephone calls. The fact that this intervention was home-based increases the portability of the intervention. Intervention portability is important so that the intervention can be implemented in health care and community settings so that the maximum number of breast cancer survivors can benefit. Further enhancing the ability to translate this intervention into these settings is the fact that it did not require specialist exercise equipment or face-to-face physical activity supervision by exercise professionals. Moreover, support staff in a health care setting or community volunteers could successfully deliver the intervention after appropriate training, and because the telephone calls were relatively brief they represent a minimal burden to staff. Thus, this intervention represents

an important step toward developing cost-effective and feasible interventions that can help a large number of breast cancer survivors to engage in sufficient levels of physical activity.

This study was not without its limitations. We did not control for the increased risk of type I errors when making multiple comparisons. Moreover, given the 26 secondary comparisons, our study is subject to at least one false discovery by chance if all of these comparisons were actually null. The reliance of self-report physical activity rather than objective measures to assess changes in physical activity can be seen as a limitation. Self-report measures, such as IPAQ, require participants to recall past activity, are a subjective means of estimating individual physical activity levels and are reliant on the individuals' ability to remember levels of exposure (Watkinson et al., 2010). The IPAQ assesses physical activity performed in the seven days prior to assessment, therefore, it is possible that the monitoring period at baseline and post-intervention may not have been representative of physical activity during the entire 6-month intervention. Self-report measures are also at risk of social desirability bias, which describes when participant responses reflect a social desirably outcome. In this case, participants self-reported physical activity levels may be higher than the actual levels performed. However, we would have expected this bias across both groups given that the participants in the usual care group were not discouraged from taking part in physical activity. Furthermore, recent research has suggested that there is minimal evidence of social desirability for self-reported physical activity measures (Motl et al., 2005).

The higher physical activity levels reported by the usual care group at baseline were a concern. Although our eligibility criteria ensured both groups completed treatment a similar number of weeks before the initial assessment, and our stratified randomisation process allocated the same number of participants who had completed chemotherapy into each group, we did not have specific eligibility criteria or did not apply stratification to randomisation based on physical activity levels. Therefore, the study was at risk of having groups with differing physical activity levels at baseline. However, the higher self-reported physical activity levels of the usual care group were not indicative of a generally higher physical activity level across all participants in the usual care group compared to the intervention group; rather, it was largely the result of three participants in this group who reported much higher activity levels (≥5000 MET-min·wk^{-1}) compared to other participants. Therefore, with the exception of these three participants the levels of physical activity were similar in both groups, as evidenced by the number of participants in the low and moderate activity physical activity categories in each group.

In addition to the higher physical activity levels at baseline, there was evidence of contamination of the usual care group. Six of the usual care group increased their physical activity levels enough to move to a higher physical activity category from baseline to post-intervention. This contamination may have been because we informed participants in the usual care of the current recommended physical activity guidelines and did not discourage them from engaging in physical activity. We felt that it would be unethical to prevent participants from engaging in a physical activity, given the disease risk associated with sedentary lifestyles. In

addition, it is likely that because ours was a physical activity trial it would attract breast cancer survivors who were interested in commencing or increasing their physical activity levels. Therefore, the usual care participants who increased their physical activity levels may have done so because of a greater state of “readiness” to engage in physical activity. This finding is consistent with a previous study, which found that breast cancer patients beginning adjuvant therapy increased physical activity more when given physical activity recommendations compared to patients who did not receive such recommendations (Jones et al., 2004). Nevertheless, despite possible usual care group contamination, we found significant improvements in total physical activity in the intervention group compared to the usual care group and more participants moved to a higher physical activity category in the intervention group compared to the usual care group over the study period.

It is possible that the significant changes in HRQoL found in the intervention group compared to the usual care group could in part be explained by the greater attention we gave the intervention group participants. Participants in this group received approximately 75 minutes more attention in the form of face-to-face and telephone counselling, compared to the participants in the usual care. Subsequent studies should attempt to balance the attention given to both groups in order to minimise the possibility of attention bias influencing results.

It is unclear whether the hormone therapy status of the breast cancer survivors influenced our finding that physical activity favourably altered lipid profiles. Evidence suggests that Tamoxifen may favourably alter lipid

profiles, while aromatase inhibitors may have a negative effect on lipid profile, although the evidence for this is less clear (Hozumi et al., 2011). We did not gather data on the hormone therapy status of participants, and therefore, we cannot rule out that this may have influenced our findings. However, because we balanced the groups in regard to chemotherapy treatment and the group were similar in age and most other characteristics, it is probable that the groups did not differ in regards to hormone therapy status.

Although the randomisation was performed by an independent clinical trials unit, the outcome assessor was not blinded to the allocation of participants. This would have been difficult as the primary investigator was responsible for delivering both the face-to-face and telephone counselling sessions and for performing the outcome assessments. Therefore, we cannot rule out the possibility that measurement bias influenced our results. Measurement bias can be introduced if the outcome assessor consciously or unconsciously provides more encouragement during assessments to the participants in the intervention group than those in the usual care group, which may result in more favourable scores in the intervention group. However, every attempt was made to standardise protocols across groups and the outcome assessor was carefully trained and monitored for objective and consistent administration of protocols. While attempts were made to reduce measurement bias attributed to the outcome assessor, the inability to blind participants to group allocation was not possible. This inability to blind participants is an inherent limitation of physical activity studies, which may bias participant responses and

behaviours because of their awareness of the study purpose and desire to please the study research staff.

There is a suggestion that the trial may have potentially been influenced by recruitment (selection) bias. Our trial attracted breast cancer survivors with an average younger age compared to the average age of breast cancer survivors (53 y vs. 61 y) (Howlader et al., 2013). Furthermore, when using the self-report IPAQ “moderate” and “high” physical activity categories to identify participants meeting current recommended physical activity guidelines, a greater number of participants in this current trial were meeting these guidelines compared to the general English population (~82% vs. 40%) (Roth, 2009). However, Bauman and colleagues (2009) recommend using the “high” IPAQ category to identify those meeting physical activity recommendations. Use of the “high” category in this way would have resulted in a much lower number of participants not meeting physical activity guidelines compared to the general English population (13% vs. 40%) (Roth, 2009). This finding would be consistent with US-based research reporting generally lower physical activity among breast cancer survivors (Irwin et al., 2003; Irwin et al., 2004).

However, because participants knew they were being recruited to a physical activity trial it is possible that the participants who were eligible and consented to taking part were those participants who were already interested in physical activity and thus, more susceptible to change. This may limit the generalizability of our results to breast cancer survivors ready to perform higher levels of physical activity. Further limiting the

generalisability of our results was the homogeneity of our sample. The majority of participants were white British (95%), non-smoking (94%), married (74%) women with children (86%) who did not have a family history of breast cancer (81%). Therefore, further research is required to establish the generalisability of results to non-white breast cancer survivors, in particular.

Future studies are needed to investigate the generalizability of findings observed in this current study and similar previous studies to, in particular, ethnic minority populations, for which the cultural barriers to engaging in physical activity may differ from those of the predominantly Caucasian samples used in previous research. Objective assessments of physical activity should be used in combination with self-report to allow for a more precise measurement of physical activity patterns amongst participants in future trials. Subsequent studies should attempt to balance the attention given to both intervention and usual care groups to minimise the effects of attention bias. It is also important to establish the cost-effectiveness of such physical activity interventions given the increased burden on health care services. The cost-effectiveness of physical activity trials could be assessed by comparing the costs of running these interventions to the possible cost-saving effects of such trials, which may include outcomes such as reduced hospital admissions and usage of health care services in the years following treatment. In addition, assessment of physical activity maintenance after study completion are required to understand whether breast cancer survivors adhere to physical activity guidelines once they have left the study interventions. This type of longitudinal physical activity follow-up study is also required to measure to effects of consistent

physical activity on recurrence, late treatment effects, such as cardiotoxicity, and breast cancer-related and all-cause mortality in a randomised controlled study design.

5.3.6 CONCLUSIONS

Within the context of the limitations of this study, we found that a home-based physical activity intervention resulted in significant favourable effects on self-reported physical activity, body mass, BMI, HRQoL, TC and LDL-C. Future research will be needed to establish the generalisability and maintenance of physical activity post-intervention. Further investigation is required to elucidate to impact of aerobic exercise interventions on glucose-insulin dynamics within breast cancer survivors. The portability and feasibility of this current intervention makes it a promising intervention that could benefit a large number of breast cancer survivors, therefore, it will be important to assess whether modifications would be needed when employed in older and perhaps less motivated breast cancer survivors. Future prospective longitudinal studies are needed to determine the impact of physical activity on recurrence and survival in breast cancer survivors.

5.4 The effects of a home-based physical activity intervention on cardiorespiratory fitness in breast cancer survivors

5.4.1 ABSTRACT

Introduction: Low cardiorespiratory fitness is inversely correlated with breast cancer-related deaths and cardiovascular and all-cause mortality. Breast cancer survivors have presented lower cardiorespiratory fitness compared to their age matched healthy, sedentary non-cancer peers. Meta-analyses have found significant improvements in cardiorespiratory fitness in breast cancer populations participating in physical activity interventions. However, these physical activity interventions typically involve supervised exercise programmes, which are costly to run and time-consuming. Therefore, the aim of this current study was to investigate the effects of a home-based intervention aimed at improving the physical activity levels of breast cancer survivors on cardiorespiratory fitness.

Methods: Thirty two (40%) breast cancer survivors (height=162±5.4 cm; mass=70.6±10.3 kg; BMI=27.2±4.4 $kg \cdot m^2$) were randomly allocated from the parent study (study 5.3).In addition to the outcomes described in study 5.3, the cardiorespiratory fitness (peak oxygen uptake, VO_2 peak) of participants allocated to the substudy was assessed by a graded exercise test using gas exchange analysis. Primary outcomes were change in VO_2 peak, body mass and self-report physical activity levels. The intervention group received an intervention aimed at encouraging the achievement of current recommended physical activity guidelines of 150 $min \cdot wk^{-1}$ of moderate physical activity. The intervention consisted of a face-to-face physical activity consultation during the first visit, followed by support telephone calls at the end of months one, two and three, and a physical

activity reminder postcard during the last two months. Ethical approval was obtained from the Black Country NHS Research Ethics Committee (West Midlands, UK).

Results: Mean VO_2 peak (25.3±4.7 $ml \cdot kg^{-1} \cdot min^{-1}$) of the breast cancer survivors was classified as "poor" compared age and gender group matched normative values. We observed a significant moderate to large improvement in relative VO_2 peak ($ml \cdot kg^{-1} \cdot min^{-1}$) (mean difference, MD, 2.1; p=0.035, d=0.8), but not in absolute VO_2 peak ($L \cdot min^{-1}$) (mean difference, 107.4; p=0.086, d=0.7) from baseline to post-intervention in the intervention group compared to usual care group. We found non-significant in other test variables, body mass and self-report physical activity outcomes. Although, based on the effect size, 64% of the pre-post-intervention increases in total physical activity in the intervention group would be above the average increase in the usual care group.

Conclusion: We found significant moderate to large increases in relative cardiorespiratory fitness as a result of a home-based physical activity intervention, but future adequately powered trials are required to confirm this finding. Our data highlights the potential efficacy of a home-based physical activity intervention coupled with face-to-face counselling and telephone support in providing beneficial effects on cardiorespiratory fitness, which may influence breast cancer outcomes and CVD risk.

5.4.2 INTRODUCTION

Breast cancer is the most common malignancy in UK women, with an average of 48,988 new cases diagnosed per year during 2008 and 2010 (ONS, 2012). Although the incidence rates of breast cancer in UK have

increased by 4.4% (2,148 new cases) from 2006 to 2008, improvements in early detection and treatment have resulted in substantial survival gains with breast cancer-specific mortality decreasing by 3% between 2006-08 and 2008-10 and by 9.3% from 2000 to 2010 (ONS, 2012; 2011). As a result, 296,037 (790.8 per 100,000 women) UK women are now living with a previous history of breast cancer within the past 10 years (NCIN, 2010), with survival times in most breast cancer patients sufficient to increase their risk for CVD.

Women diagnosed with breast cancer experience an excess of cardiovascular mortality (Eloranta et al., 2012). A recent retrospective cohort study, consisting of 63,566 breast cancer patients followed up for a median of nine years, found that CVD was the primary cause of death (15.9%, 95% CI 15.6-16.2) followed closely by breast cancer (15.1%, 95% CI 14.8-15.4) (Patnaik et al., 2011). The authors (2011) reported that CVD increased breast cancer-specific mortality by 24%, which may have been due to the cardiac toxicity associated with chemotherapy in breast cancer patents (Jones et al., 2007), and potentially under-diagnosis and under-treatment of CVD for breast cancer patients, because their primary cancer diagnosis may be perceived as the overriding medical priority. In addition to this, the increased mortality due to CVD could be attributed to the higher number of women who survive breast cancer, who as they grow older are more likely to have comorbidities, and women with more comorbidities are more likely to die as a result of causes other than breast cancer (CDC, 2010; 2007).

Higher levels of physical activity are associated with improved survival and fewer recurrences in women diagnosed with breast cancer (Beasley et al., 2012; Ibrahim and Al-Homaidh, 2011) and has also been recommended as an intervention to improve CVD risk profile (Knobf and Coviello, 2011; Thompson et al., 2003). Furthermore, low cardiorespiratory fitness, usually measured by oxygen uptake at maximal or peak exercise (VO_2 max or peak), has been shown to be inversely correlated with breast cancer-related deaths and cardiovascular and all-cause mortality (Blair et al., 1996; Blair et al., 1989; Peel et al., 2009). Women with low cardiorespiratory fitness of below eight maximal metabolic equivalents (METs, where 1 MET=VO_2 of 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$) or a VO_2 max of 28 $ml \cdot kg^{-1} \cdot min^{-1}$ had a nearly three-fold increase in breast cancer deaths compared to those who reached 10 METs (VO_2 max of 35 $ml \cdot kg^{-1} \cdot min^{-1}$) or greater (Peel et al. 2009). Therefore, it is worrying that a recent study indicated breast cancer survivors had a 22% lower VO_2 max compared to their age matched healthy, sedentary non-cancer peers (Jones et al., 2012).

Previous systematic reviews and meta-analyses have found significant improvements in cardiorespiratory fitness in breast cancer populations participating in physical activity interventions (Fong et al., 2012; McNeely et al., 2006). The results of the systematic review and meta-analysis conducted as part of the current thesis (see section 2.8) found greater improvements in the cardiorespiratory fitness of breast cancer survivors within aerobic exercise interventions. However, physical activity interventions involving breast cancer populations typically involve supervised exercise programmes, which are costly to run and time-consuming. Therefore, given that health care resources are finite, cost-

effective interventions that can improve the health of patients are more desirable to those making clinical, managerial and policy decisions. Several studies have found encouraging increases in cardiorespiratory fitness in breast cancer survivors utilising low-cost home-based physical activity interventions (Rogers et al., 2009; Fillion et al., 2008; Pinto et al., 2005). Therefore, the aim of this current study was to investigate the effects of a home-based intervention focused on improving physical activity levels of breast cancer survivors on cardiorespiratory fitness.

5.4.3 METHOD

Trial design

This current study was a two-armed, parallel design RCT that compared a six month home-based physical activity intervention to usual care. Individualised face-to-face consultations and telephone counselling to personalise goal-setting and assess progress formed the key components of our intervention. The current study presents the data from a substudy within the trial outlined in section 5.3. Forty per cent of the patients randomised to intervention and usual care groups in the parent study were randomised to a substudy involving an exercise tolerance test and blood pressure assessment in addition to all of the same outcome assessments administered as part of the parent study. The current study reports data collected at baseline and six months. Recruitment of participants took place between January 2010 and March 2013.

Participants

Women attending breast cancer clinics at Russells Hall Hospital (The Dudley Group of Hospitals, NHS Trust, UK), were invited to enrol on the

study by cancer care nurses working within these clinics. Interested patients were given a study information booklet and were contacted by the primary researcher via telephone a week later. The eligibility criteria have been described earlier in the methods of study 5.3 (please see pg. 330). The study was reviewed, approved and monitored by the investigational review boards of the Russells Hall Hospital and all subjects provided written consent prior to data collection.

Participants were asked to visit the testing venue (Research and Development Unit, Russells Hall Hospital, Dudley) on two separate occasions at baseline and post-intervention. On the initial visit participants reported to the testing venue early in the morning following a 12 hour overnight fast. Upon arrival on the initial assessment day, participants' height, mass and body composition were assessed. Participants were then asked to complete a demographics questionnaire, followed by the IPAQ and the FACT-B HRQoL questionnaire. Upon completion of the questionnaires participants had a venipuncture blood sample taken. For those participants who had been allocated to the cardiorespiratory fitness substudy an additional day and time (within 5 days of first assessment) was organised in order to complete an exercise tolerance test. Prior to exercise tolerance testing patient notes were reviewed by the author (IL) and the patients' breast surgeon in order to establish whether they were any contraindications to engage in physical testing and activity. Before exercise testing, participants were asked to refrain from vigorous exercise the day before, to have eaten at least three hours before the test and to be normally hydrated pre-test. Participants were asked not to change their normal physical activity patterns from when the appointment was arranged

to the day of the two appointments. All participants were subjected to the same data collection procedures overseen by the same investigator.

Home-based physical activity Intervention

Following consent and randomisation, breast cancer patients in the intervention group received an intervention aimed at encouraging the adoption of a more physically active lifestyle. This intervention was described in detail in study 5.3. In brief, participants received a face-to-face consultation, followed by a support telephone call at the end of months one, two and three. During the last two months (4 and 5) patients received physical activity reminder leaflets encouraging their participation in home-based physical activity. The initial goal of the intervention (months 1-3) was for participants to progress towards accumulating 30 minutes of moderate intensity exercise on three to five days per week. During month's three to six, the intervention participants were encouraged to work towards accumulating at least 30 minutes of moderate-intensity physical activity on five to seven days per week in broad agreement with current public health guidelines (Bull and the Expert Working Groups, 2010).

Since not informing patients about the benefits of physical activity may be considered unethical, participants randomised to the usual care arm received standard information regarding physical activity (i.e. the current recommended physical activity guidelines), as provided to all breast cancer patients treated at the site. Participants completed the same baseline and post-six month intervention assessments as the physical activity intervention group.

Study outcomes

The outcomes reported in the current study include cardiorespiratory fitness as assessed via an exercise tolerance test, blood pressure and self-reported physical activity (assessed via IPAQ). The primary outcome of the current study was cardiorespiratory fitness (VO_2 peak). Secondary outcomes included time to exhaustion (TTE), peak heart rate (HR peak), blood pressure at rest and total, leisure, moderate and vigorous physical activity (MET-min·wk^{-1}). All assessments were made at baseline and within two weeks of completing the six-month intervention. The details of these assessments are described in chapter 4.3.

Statistical analysis

Only data from breast cancer survivors who had attended their initial assessments were included in the analysis. All data was inputted onto to a Microsoft Excel™ spreadsheet (Microsoft Corporation) and transferred to Statistical Package for Social Sciences (SPSS) (IBM™) for windows version 20.0 for analysis. For all analyses, we employed the intention-to-treat (ITT) approach (Newell et al., 1992). Physical activity data outliers were identified by converting all scores to z-scores. Z-scores greater than 3.29 were classed as outliers, values above this score were converted to one unit smaller than the next highest score with a z-score below 3.29 (Tabachnik and Fidell, 2007). The distribution of all continuous, baseline and post-intervention outcomes were assessed using the same method outlined in study 5.3. Of the variables, all exercise tolerance test variables and blood pressure were normally distributed at both baseline and post-intervention. Normally distributed variables were expressed as mean ± *s*,

while all other variables were described using medians (IQR). Categorical data were presented as number of participants and percentages.

To correct for non-normal distributions, variables not normally distributed were log transformed. The physical activity data contained zero values, and were therefore, transformed to log10(X+1). Repeated-measures linear mixed model analysis was performed on all continuous trial outcomes to assess differences in group changes from baseline to post-intervention (i.e. 6-months from baseline). The rationale and description of this statistical test were provided in study 5.3. Statistical tests and corresponding p values were two-sided; a p-value of less than 0.05 was reported as statistically significant. Cohen's d effect sizes for linear mixed model analysis was calculated based on the estimate comparing baseline values of the intervention group to the 6-month values in the intervention group and the baseline and 6-month values for the usual care group. Effect sizes for the t-values of each comparison were calculated by converting the t value to d using the formula provided in study 5.3 (pg. 341). According to Cohen (1992) a small effect is denoted as d=0.2, medium effect d=0.5 and large effect d=0.8. For the purposes of this report, effect sizes of <0.20 were interpreted as small, 0.2 to <0.5 as small to moderate, 0.5 to <0.8 as moderate to large, and ≥0.8 as large.

5.4.4 RESULTS

Flow of participants through the trial and recruitment

Eighty participants were recruited for the parent trial between January 2010 and March 2013 (see section 5.3). Flow of participants through the study is provided in Figure 5.4.1. Forty participants each were randomised

to the intervention and usual care groups, and of the forty participants in each group 40% (16 in each group) were randomly allocated to the cardiorespiratory fitness substudy presented here. Twenty nine of the substudy participants completed the trial, with 15 and 14 completers in the intervention group and usual care group, respectively. One participant assigned to the intervention group dropped out of the trial due to a recurrence of breast cancer, while of the two participants assigned to the usual care group, one dropped out of because she did not want to return to the hospital for reassessment and the other participant was not contactable and as such was lost to follow-up.

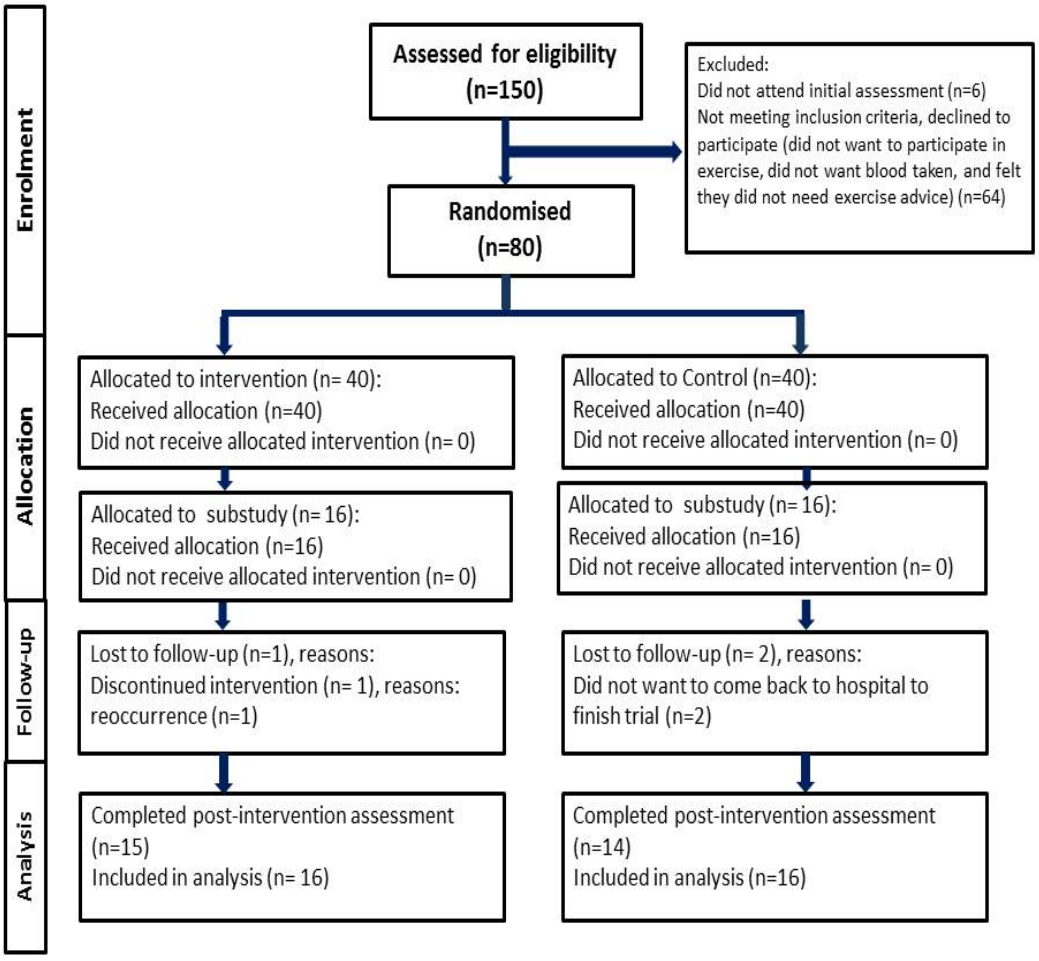

Figure 5.4.1 Flow of participants through the trial

Table 5.4.1 Personal characteristics of the participants at baseline (intervention, n=16; usual care, n=16)

	N (%) overall	N (%) intervention	N (%) usual care
Mean±*s* age (y)	52.3±9.6	52.5±10.7	52.0±8.6
Mean±*s* time since diagnosis (wk)	40.6±24.5	41.3±25.5	39.9±25.4
Mean±*s* time since end of treatment (wk)	10.9±9.2	10.1±9.4	11.6±11.6
Ethnic Origin:			
o White British	32 (100)	16 (100)	16 (100)
BMI ($kg \cdot m^2$):			
o Obese (BMI=≥ 30)	8 (25)	5 (31)	3 (19)
o Overweight (BMI=25-29.9)	12 (38)	6 (38)	4 (25)
o Normal (BMI=18-24.9)	12 (38)	5 (31)	7 (44)
o Underweight (BMI=< 18)	0 (0)	0 (0)	0 (0)
Family History of breast cancer:			
o Yes	6 (19)	3 (19)	3 (19)
o No	26 (81)	13 (81)	13 (81)
Smoking:			
o Current	1 (3)	0 (0)	1 (6)
o Previously	11 (34)	2 (30)	9 (56)
o Never	20 (63)	14 (70)	6 (38)
o Mean±*s* cigarettes/day	3.9±6.5	0.9±2.4	7.0±7.8
o Mean±*s* years smoking	15.8±13.2	21.0±12.7	14.8±13.8
Alcohol drinkers:			
o Yes	25 (78)	11 (69)	14 (88)
o No	7 (22)	5 (31)	2 (12)
Mean±*s* no. of days/week when alcohol is drank	2.5±1.5	2.5±1.6	2.6± 1.5
Mean±*s* no. glasses on days when drinking most	2.5±1.5	2.5±1.8	2.6±1.4
Drink type :			
o Wine	20 (80)	9 (88)	11 (81)
o Beer	2 (8)	1 (6)	1 (6)
o Spirits	3 (12)	1 (6)	2 (13)
Co-morbidities:			
o Diabetes	1 (3)	1 (6)	0 (0)
o Hypertension	4 (13)	3 (18)	1 (6)
o High Cholesterol	3 (9)	2 (13)	1 (6)
o Heart disease	2 (6)	1 (6)	1 (6)
o Vascular disease	1 (3)	0 (0)	1 (6)
o Asthma or chronic bronchitis	4 (13)	1 (6)	3 (18)
o Osteoarthritis	6 (19)	2 (13)	4 (25)
o Rheumatoid arthritis	2 (6)	1 (6)	1 (6)
o Kidney disease	2 (6)	0 (0)	2 (13)
o Liver disease	1 (3)	0 (0)	1 (6)
Parity:			
o Nulliparous	4 (13)	1 (6)	3 (18)
o Parous	28 (87)	15 (94)	13 (82)
Number of children:			
o 1	4 (13)	1 (6)	3 (19)
o 2	22 (69)	12 (75)	10 (81)
o 3	1 (3)	1 (6)	0 (0)
o 4	1 (3)	1 (6)	0 (0)

	N (%) overall	N (%) intervention	N (%) usual care
Mean±age at birth of first child (y):	24.3±10.4	25.4±8.3	23.3±12.3
Breast fed children:			
o Yes	16 (50)	7 (44)	9 (44)
o No	16 (50)	9 (56)	7 (56)
Currently menstruating:			
o Yes	7 (22)	3 (19)	4 (25)
o No	25 (78)	13 (81)	12 (75)
Oral Contraceptive use (current/previous):	27 (84)	12 (75)	15 (97)
o Yes	5 (16)	4 (25)	1 (3)
o No	9.8±7.2	9.5±8.3	10.1±6.3
o Mean±*s* years taken			
HRT:			
o Never	26 (81)	14 (87)	12 (75)
o Previously/Currently	6 (19)	2 (13)	4 (25)
o Mean±*s* years taking HRT	6.8±5.8	6.0±2.8	7.3±7.3
Marital Status:			
o Single	2 (6)	1 (6)	1 (6)
o Married	25 (78)	14 (80)	11 (68)
o Not married, living with partner	2 (6)	1 (6)	1 (6)
o Divorced or separated	3 (9)	0 (0)	3 (19)
Highest qualification:			
o O-levels or GCSE	11 (34)	5 (31)	6 (38)
o A-level or equivalent	4 (13)	3 (19)	2 (5)
o NVQ	5 (16)	1 (6)	4 (25)
o College degree or diploma	7 (22)	4 (25)	3 (13)
o Bachelor degree	1 (3)	1 (6)	0 (0)
o Post-graduate degree	1 (3)	0 (0)	1 (6)
o Other or not listed	3 (9)	2 (13)	1 (6)
o Mean age±*s* years leaving school	16.9±2.0	16.6±1.9	17.1±2.2
Employment status:			
o Employed full-time	5 (16)	3 (19)	2 (13)
o Employed part-time	12 (38)	6 (38)	6 (38)
o Homemaker	3 (9)	2 (13)	1 (6)
o Unemployed	1 (3)	0 (0)	1 (6)
o Unable to work due to illness	1 (3)	0 (0)	1 (6)
o Retired	8 (25)	5 (31)	3 (19)
o Missing	1 (3)	0 (0)	1 (6)
Physical activity:			
o Low	9 (28)	4 (25)	5 (31)
o Moderate	19 (59)	12 (75)	7 (44)
o High	4 (13)	0	4 (25)

Table 5.4.2 Linear mixed model results for exercise tolerance test (ETT), body mass and physical activity (PA, MET-min·wk^{-1}) variables comparing intervention group to usual care group at baseline to post-intervention†

	Intervention group (n=16)			Usual care group (n=16)					
	Baseline	**Post-intervention**	**Ave diff**	**Baseline**	**Post-intervention**	**Ave diff**	**Estimate statistic***	**95% CI**	**p-value (d)**
VO_2 peak (ml·min^{-1})	1749±311	1795±315	46	1816±264	1852±223	36	-107.4	-231.2 to 16.4	0.09 (0.7)
VO_2 peak (ml·kg^{-1}·min^{-1})	24.5±4.6	25.8±5.6	1.3	26.6±4.4	26.6±3.3	0	-2.1	-4.1 to -1.6	**0.04 (0.8)**
Time to Exhaustion (sec)	471±105	531±100	60	523±76	545±49	22	-34.2	-84.6 to 16.3	0.18 (0.5)
Peak Heart rate (bpm)	176±11	181±9	5	174±16	174±16	0	-4.1	-9.2 to 1.0	0.11 (0.6)
Resting SBP (mm·Hg^{-1})	125±10	126±14	1	127±13	126±12	-1	-3.0	-10.5 to 4.6	0.41 (0.3)
Resting DBP (mm·Hg^{-1})	78±6	78±8	0	81±9	78±6	-3	-3.8	-8.6 to 1.2	0.13 (0.6)
Resting MAP (mm·Hg^{-1})	97±10	98±14	1	99±11	96±9	-3	-4.4	-11.1 to 2.3	0.20 (0.5)
Mass (kg)	72.5±12.4	71.0±12.7	-1.5	69.0±8.3	70.1±7.0	1.1	1.04	-1.9 to 4.0	0.48 (0.3)
Total PA‡	604 (1058)	1388 (661)	784	1313 (2023)	1497 (1623)	184	-0.16	-0.42 to 1.0	0.21 (0.5)
Leisure PA‡	308 (569)	792 (572)	484	428 (930)	594 (896)	166	-0.38	-1.41 to 0.72	0.51 (0.2)
Walk PA‡	404 (637)	752 (726)	348	347 (404)	545 (743)	198	0.19	-0.57 to 0.96	0.61 (0.2)
Moderate PA‡	202 (961)	586 (636)	384	599 (946)	819 (1651)	220	-0.39	-1.05 to 0.28	0.25 (0.4)
Vigorous PA‡	0 (0)	0 (320)	0	0 (270)	0 (180)	0	-0.59	-1.80 to 0.62	0.33 (0.4)

Ave diff= average difference; Descriptive statistics presented as either mean±*s* or median (interquartile range) depending on distribution of data;
† Post-intervention data were only available for the 15 participants in the intervention and the 14 participants in the usual care
*The effect estimate represents the statistical difference between intervention and usual care groups pre-post-intervention, therefore, positive values represent higher than scores at baseline in the intervention group, while negative values represent lower scores at baseline in the intervention group.
‡ Physical activity effect estimates, 95% CI, p-value and Cohen's d based on linear mixed model analysis on data log transformed base 10, log10(X)
Significant results in bold

Participant characteristics at baseline

Table 5.4.1 provides the baseline characteristics overall and by group assignment. Baseline data was collected from 32 breast cancer survivors (height=162±5.4 cm; mass=70.6±10.3 kg; BMI=27.2±4.4 kg·m^2) who have completed the 6-month study duration. Both the intervention group (height=160±4.5 cm; mass=72.2±12.0 kg; BMI=28.2±4.9 kg·m^2) and the usual care group (height=163±6.0 cm; mass=68.9±8.3 kg; BMI=26.1±3.6 kg·m^2) consisted of 40 participants. Sixteen (50%) patients had undergone chemotherapy, with an equal number of participants who had received chemotherapy in each group. The baseline characteristics of participants in the intervention and usual care groups were similar in terms of age, mean time since diagnosis and end of treatment, and other demographic and lifestyle factors (see table 5.4.1).

Cardiorespiratory, body mass and physical activity outcomes

Analysis of cardiorespiratory fitness revealed that the breast cancer survivor's baseline mean VO_2 peak was 25.3±4.7 ml·kg^{-1}·min^{-1}, with a median percentile of 20 (IQR=23.8) when each participants scores were compared to age and gender group matched normative values (ACSM, 2009). The 20th percentile is described as a poor cardiorespiratory fitness. We observed a significant moderate to large improvement in cardiorespiratory fitness in relative terms (ml·kg^{-1}·min^{-1}) from baseline to post-intervention in the intervention group compared to usual care group (mean difference, 2.1; p=0.035, d=0.8). The interpretation of the Cohen's d indicates that 79% of the usual care group's change in relative VO_2 peak was below that of the average VO_2 peak change in the intervention group. However, no significant improvement was observed for cardiorespiratory

fitness in absolute terms ($L \cdot min^{-1}$) (mean difference, 107.4; p=0.086, d=0.7). Although, the large effect size indicates that 76% of participants in the usual care group increased their absolute VO_2 peak by less than the participants in the intervention group. We found no significant differences between groups in TTE, HR peak or blood pressure at baseline versus post-intervention (see Table 5.4.2). Similarly, no differences were found in the physical activity group compared to the usual care group over the 6-month intervention period for body mass and total, leisure, walking, moderate and vigorous physical activity (p>0.05). Although, based on the effect size, 64% of the increases in total physical activity from baseline to post-intervention in the usual care group would be below the average increase in the intervention group.

5.4.5 DISCUSSION

In our subset of breast cancer survivors, we found significant improvements in cardiorespiratory fitness (VO_2 peak, $ml \cdot kg^{-1} \cdot min^{-1}$) in a physical activity intervention group compared to a usual care group. However, we found no significant improvements in absolute VO_2 peak values, TTE, HR peak, blood pressure or physical activity levels in participants in the intervention group compared to usual care.

The mean VO_2 peak values of the breast cancer survivors in this current study are similar to that reported in previous studies in which cardiorespiratory fitness was measured directly (Burnett et al., 2013; Jones et al., 2012; Mehnert et al., 2011; Peel et al., 2009; Fillion et al., 2008; Herrero et al., 2006; Hutnick et al., 2005; Courneya et al., 2003). The low VO_2 peak values reflect the poor physical condition of our breast

cancer survivors, and were lower than the values (28 $ml \cdot kg^{-1} \cdot min^{-1}$) Peel et al. (2009) associated with a three-fold increase in risk of breast cancer mortality. Therefore, the values reported in the current study may indicate an increased risk of breast cancer mortality and the need for this population to engage in physical activity to improve cardiorespiratory fitness and overall health status.

In the current study, breast cancer survivors in the intervention group significantly improved cardiorespiratory fitness compared to the usual care group. We found increases in VO_2 peak values of 5.3% in the physical activity intervention group, compared to no change (0%) in the usual care group. The magnitude of this treatment effect was lower compared to the 9% to 17% increases observed in previous studies assessing the effect of physical activity on VO_2 peak in breast cancer survivors (Mehnert et al., 2011; Fillion et al., 2008; Herrero et al., 2006; Hutnick et al., 2005; Courneya et al., 2003). However, all of the studies above consisted of supervised exercise interventions; therefore, the improvements observed in cardiorespiratory fitness in the current study are encouraging given the home-based nature of the intervention. Moreover, we observed non-significant increases in physical activity levels in the intervention compared to usual care, thus, it is likely that improvements in cardiorespiratory fitness may have been greater if larger increases in physical activity levels were observed. In addition, the participants in the usual care maintained VO_2 peak values, which suggest that the exercise tolerance test may have acted as a source of motivation to engage in physical activity over the study period. Nevertheless, the improvements in VO_2 peak in our intervention group may improve participants' ability to perform normal day

to day activities, increase independence, promote a sense of well-being and ultimately confer a positive influence on breast cancer mortality (Peel et al., 2009; Herrero et al., 2006).

In the current study, the lack of improvement in relative VO_2 peak observed in the usual care group, despite a slight non-significant improvement in absolute VO_2 peak can almost entirely be attributed to non-significant increase in body mass (i.e. the increase in absolute VO_2 peak was equivalent to the increase in body mass). However, the significant increase in relative VO_2 peak observed in the intervention group can only partially be explained by a reduction in body mass, given the non-significant improvements in absolute VO_2 peak (i.e. the increase in relative VO_2 peak was higher than that expected for the reduction in body mass observed). Therefore, mechanisms other than reduced body mass may be responsible for the improvements in relative VO_2 peak observed in the intervention group. The mechanisms by which physical activity can increase VO_2 peak in breast cancer survivors remains to be elucidated. However, previous studies of postmenopausal women attributed physical activity-induced increases in VO_2 peak to adaptations in skeletal muscles (Spina et al., 1993; 2000). Adaptations associated with prolonged aerobic exercise, such as a greater left ventricular ejection fraction resulting from a more compliant cardiac chamber, increased oxidative enzyme activity, capillary density, myoglobin concentrations, muscle glycogen and higher percentage of type I fibre types, facilitate improvements in cardiac output and arterial-venous oxygen difference, which can in turn improve VO_2 peak (Levine, 2008; Bassett and Howley, 2000; Holloszy and Coyle, 1984). Thus, it is probable that both increases in cardiac output and

arterial-venous oxygen difference contributed to the physiologic adaptations observed in this current trial. However, because we measured VO_2 peak and not VO_2 max, we cannot discount the possibility that psychological factors, such as increased motivation, self-confidence and tolerance, influenced the pre-post intervention changes in VO_2 peak.

The strengths and limitations of our trial merit comment. Strengths include the RCT design, validated measures of VO_2 peak and the relatively brief and inexpensive, highly feasible and home-based nature of the intervention. The limitations of the parent study have been described in study 5.3, therefore, only the specific limitations of the substudy will be discussed in this section. The outcome assessor was not blinded to the allocation of participants, which was not possible as the primary investigator was responsible for delivering the face-to-face and telephone counselling sessions and for performing the outcome assessments. Therefore, we cannot rule out the possibility that measurement bias influenced our results. Measurement bias can be introduced if the outcome assessor consciously or unconsciously provided more encouragement during exercise tolerance tests to the participants in the intervention group than those in the usual care group, which may have resulted in more favourable scores in the intervention group. Breath-by-breath systems can have a typical measurement error of approximately 2%, and therefore, may account for a portion of the 5% improvement in VO_2 peak observed in the intervention group (Lamberts et al., 2009). However, every attempt was made to standardise protocols across groups and the outcome assessor was carefully trained and monitored for objective and consistent administration of exercise test protocols. While

attempts were made to reduce measurement bias attributed to the outcome assessor, the blinding of participants to group allocation was not possible. This inability to blind participants is an inherent limitation of physical activity studies, which may bias participant responses and behaviours because of their awareness of the study purpose and desire to please the research staff.

In the parent study (see study 5.3) 36 participants were needed in each group to detect a change in physical activity with a power of 0.80 and a two-tailed alpha less than 0.05. Therefore, the substudy was not powered to detect changes in cardiorespiratory fitness in the subsample of 32 breast cancer survivors. Our finding of no significant improvements in physical activity levels despite greater increases in physical activity levels in the intervention group compared to the usual care group over the study period may have been a result of insufficient statistical power and a higher probability of type II errors. Therefore, future studies with sufficient statistical power to detect differences are required to confirm the effect of home-based physical activity on cardiorespiratory fitness in particular.

5.4.6 CONCLUSIONS

In the context of the limitations outlined above, we found significant moderate to large increases in cardiorespiratory fitness as a result of a home-based physical activity intervention. Our data highlights the potential efficacy of a home-based physical activity intervention coupled with face-to-face counselling and telephone support in providing beneficial effects on cardiorespiratory fitness, which may influence breast cancer outcomes and CVD risk. Sufficiently powered future studies are required to detect

differences between groups to confirm our finding of improved cardiorespiratory fitness in our home-based physical activity intervention. Prospective longitudinal RCTs are needed to determine the impact of physical activity and improvements in cardiorespiratory on breast cancer outcomes and development of CVD in breast cancer survivors.

CHAPTER SIX: GENERAL DISCUSSION

The aim of the current thesis was to investigate physical activity in breast cancer patients. Specifically, this project explored the awareness of the role of physical activity in breast cancer risk in an “at risk” of breast cancer population and levels of physical activity of women at different stages of the breast cancer pathway, namely, breast screening attendees (i.e. pre-diagnosis), during adjuvant therapy and post-treatment breast cancer. Subsequently, the project investigated the effects of physical activity on outcomes associated with the health and well-being of breast cancer patients’ post-treatment (i.e. breast cancer survivors). The main findings of this current thesis expand our knowledge of physical activity among women at different stages of the breast cancer pathway and emphasises the role of physical activity in improving the lives of breast cancer patients survivors.

As highlighted in the literature review, higher levels of physical activity are associated with a lower risk of developing breast cancer and both lifetime and recent (1 to 3 y) pre-diagnosis can reduce the risk of all-cause and breast cancer-related mortality. However, as indicated in the first study a relatively high proportion of the breast cancer screening attendees we sampled, were categorised as being low to moderately physically active and found to engage in low levels of recreational physical activity, despite a high level of awareness of the potential beneficial role of physical activity in reducing breast cancer risk. Furthermore, in the second study we found that physical activity was reduced in patients undergoing chemotherapy, and that the physical activity levels of breast cancer survivors were below the levels observed in breast screening attendees. Given the strong

association found, in our systematic review and meta-analysis of epidemiological studies, between post-diagnosis physical activity and reductions in all-cause and breast cancer-related mortality.

Our systematic review and meta-analysis of controlled trials investigating the effect physical activity interventions in breast cancer survivors, emphasized the beneficial effect that physical activity can have on outcomes such as self-reported physical activity, cardiorespiratory fitness, BMI, body fat %, muscular strength, systolic blood pressure, HRQoL, fatigue, self-esteem, depression and anxiety among breast cancer survivors. However, due to few available trials assessing particular outcomes, small number of participants and substantial heterogeneity of interventions implemented and measures used to assess outcomes, we could not draw conclusions on the impact of a number of outcomes such as mass, plasma glucose, insulin, HOMA and lipid concentrations. Furthermore, there was a paucity of data regarding the effectiveness of home-based physical activity interventions and interventions compromising of specific physical activity counselling in breast cancer survivors. To this author's knowledge, no UK-based trials investigating this type of intervention in British breast cancer survivors exist. Overall, the findings from the review of physical activity interventions provided a strong rationale for investigating the effects of a home-based physical activity intervention on the health and well-being of breast cancer survivors.

We conducted a RCT to explore whether a home-based physical activity intervention could be beneficial to breast cancer survivors. In this study we found that a home-based physical activity intervention with an additional

physical activity counselling component resulted in significant favourable effects on self-reported physical activity, body mass, BMI, HRQoL, TC and LDL-C. In a substudy involving 40% of the participants from the parent RCT, we observed significant increases in cardiorespiratory in the physical activity intervention compared to usual care over the study period. The results of the RCT are encouraging given the home-based nature of the intervention coupled with its counselling component. Home-based physical activity interventions are appealing in health care settings because they are relatively brief, inexpensive and highly feasible. One particular benefit of this type of intervention is its portability, it did not require specialist exercise equipment or face-to-face physical activity supervision by exercise professionals, which means that it can be implemented in a variety of health care and community settings to maximise the number of breast cancer survivors who can benefit.

Physical activity counselling aims to promote physical activity behaviour change within the physical activity interventions. Few previous physical activity interventions in breast cancer survivors have included this component in their interventions, and therefore, it can be argued that these trials have neglected to consider the long-term implications of individuals' adherence and motivation to exercise. Without the support to change physical activity behaviours beyond what is provided by the exercise facilities or the physical activity programmes, it is unlikely breast cancer survivors will be able to maintain their participation once the specified intervention period lapses. Therefore, the inclusion of a single face-to-face counselling session followed by three support telephone calls focused on promoting physical activity behaviour change and facilitating

adherence by providing encouragement and advice on overcoming barriers to physical activity. One of the key benefits of our intervention in regards to its portability was that support staff in a health care setting or community volunteers could successfully deliver the intervention after appropriate training, and because the telephone calls were relatively brief they represent a minimal burden to staff. Thus, this intervention may represent an important step toward developing cost-effective and feasible interventions that can help a large number of breast cancer survivors to engage in sufficient levels of physical activity.

The portability and feasibility of this current intervention makes it a promising intervention that could benefit a large number of breast cancer survivors, therefore, it will be important to assess whether modifications would be needed when employed in older and perhaps less motivated breast cancer survivors. Further investigation is required to elucidate to impact of aerobic exercise interventions on glucose-insulin dynamics within breast cancer survivors. Given the increases in CVD mortality in breast cancer survivors, our finding of low cardiorespiratory fitness within our sample of breast cancer survivors was worrying. Studies with sufficient power to detect differences between groups are required to confirm our finding of improved cardiorespiratory fitness in our home-based physical activity intervention group versus usual care. The cost-effectiveness of home-based physical activity should be assessed in future research. This can be achieved by comparing the costs of running this type of interventions to the possible cost-saving effects of such trials, which may include outcomes such as reduced hospital admissions and usage of health care services in the years following treatment. Future prospective

longitudinal RCTs are needed to determine the impact of physical activity and improvements in cardiorespiratory fitness on breast cancer-related mortality, recurrence and development of CVD in breast cancer survivors.

Overall, higher levels of physical activity were associated with lower all-cause and breast cancer-related mortality, with post-diagnosis physical activity providing the strongest risk reductions. Physical activity interventions may have beneficial effects on the health and well-being of post-treatment breast cancer patients. Our observational studies discovered relatively low levels of physical activity, and in particular recreational physical activity, in women at different stages of the breast cancer pathway. In particular, women undergoing chemotherapy and those who had completed breast cancer treatment had lower levels of physical activity compared to women attending breast screening. We found that a home-based physical activity intervention with an additional specific physical activity counselling component resulted in significant improvements in self-reported physical activity, body mass, BMI, HRQoL and TC and LDL-C concentrations, and significant improvements in cardiorespiratory fitness and TC concentrations in a subsample of participants. Our data supports the inclusion of physical activity promotion as an integral component for the management breast cancer survivors. The home-based physical activity intervention with an additional counselling and support component utilised in this current study provides a promising, portable and highly feasible tool that could be applied in health and community settings to improve the health and well-being of large numbers of breast cancer survivors, and potentially reduce their risk of breast cancer-related, all-cause and CVD mortality.

CHAPTER SEVEN: LIMITATIONS

Although the methodology of the present study was carefully designed, several potential limitations may have influenced our findings. Limitations are discussed in detail within each study, therefore, in this section an overview of the key limitations are presented. Limitations were listed as either general or study specific, depending on whether they affected the project as a whole or individual studies, respectively.

7.1 General limitations

- A cross-sectional design was utilised in the first and second study in the current project. Although the associations observed in these studies are interesting and can serve to generate hypotheses, they do not provide definitive evidence for causality and directionality, which can be best addressed via RCTs.
- Physical activity levels were assessed in each study via self-report (IPAQ), which requires participants to recall past activity, and is therefore, a subjective means of estimating individual physical activity levels that relies on the individuals' ability to remember levels of exposure (Watkinson et al., 2010). The IPAQ assesses physical activity performed in the seven days prior to assessment; therefore, it is possible that the monitoring period may not have been representative of participants' typical physical activity. Furthermore, physical activity questionnaires are at risk of social desirability bias, which describes when participant responses reflect a social desirably outcome. In this case social desirability bias would be manifested as higher reported physical activity. However, physical activity questionnaires tend to result in over-reporting of

physical activity rather than under-reporting (Weinstein et al., 1998), therefore, the physical activity levels presented in our studies would represent over-reported values. However, recent research has suggested that there is minimal evidence of social desirability for self-reported physical activity measures (Motl et al., 2005).

- All of the samples used in the current project were convenience samples, and therefore, expose all of the studies to selection bias, and as such our samples may not be representative of the population they were taken from. Selection bias refers to a systematic difference between a study sample and the population from which they were recruited or a systematic difference between the comparison groups within a controlled trial. Randomised recruitment sampling strategies can be used in place of convenience sampling to reduce selection bias. Furthermore, because we recruited participants to take part in physical activity studies, the group may have included participant's interested or already engaged in physical activity. Therefore, our participants may not be representative of all post-treatment breast cancer patients. However, this would likely lead to higher levels of physical activity than what might be typical for this population.
- Finally, the generalisability of our findings is limited due to the lack of ethnic diversity in our samples. Each of the participant groups consisted of 95% or more white British women, therefore, our findings are not generalisable to other ethnic groups. Furthermore, we recruited from only one geographical location, the Black Country region of the West Midlands, and thus, it cannot be assumed that findings in women from this area can be applied to all of the UK

population. However, the physical activity levels, BMI and other demographic variables were consistent with a sample of breast cancer patients taken from another location within the UK (Daley et al., 2007).

7.2 Study specific limitations

7.2.1 Study one and two

- The generalisability of our findings regarding physical activity levels of women attending breast screening and women who are receiving or have completed breast cancer treatment is limited, because our sample included only women from the Black Country area of the West Midlands in the UK. Our samples of chemotherapy and post-treatment breast cancer patients were also relatively small, which further limited our ability to generalise. Furthermore, the NHSBSP sample included in studies one and two was chosen as a "pre-diagnosis" comparison group based on their status as an "at risk of breast cancer" group. However, clearly not all of the patients sampled will develop breast cancer, and therefore, this group may not be representative of breast cancer patients pre-diagnosis.
- In study one, the BMI for the group of screening attendees was computed from self-reported height and mass. This may have influenced the data of the present study. However, self-reported BMI values tend to overestimate measured BMI values at the low end of the BMI scale (<22 $kg \cdot m^2$) and underestimate BMI values at the high end, particularly at values >28 $kg \cdot m^2$ (Stommel and Schoenborn, 2009). Therefore, because most of our sample had

BMI's at the higher end and considering the general trend in the literature towards an underestimation of BMI, it is perhaps more probable that our mean self-reported BMI represents an underestimation rather than an overestimation. Furthermore, effects of physical activity on BMI and/or the effects of the different stages of breast cancer were not amongst the main aims of the project.

7.2.2 Study three and four

- Although we utilised a stratified randomisation process to reduce selection bias (i.e. systematic differences between intervention and usual care groups) and allocate the same number of participants who had completed chemotherapy into each group, we did not have specific eligibility criteria or did not apply stratification to randomisation based on physical activity levels. Unfortunately, higher physical activity levels were reported by the usual care group compared to the intervention group at baseline. However, the higher self-reported physical activity levels of the usual care group were largely the result of three participants in this group who reported much higher activity levels (≥5,000 MET-min·wk^{-1}) compared to other participants. Therefore, with the exception of these three participants the levels of physical activity were similar in both groups, as evidenced by the number of participants in the low and moderate physical activity categories in each group.
- There was a suggestion of contamination within the usual care group, that is, six of the usual care group increased their physical activity levels enough to move to a higher physical activity category from baseline to post-intervention. This contamination may have been because we informed participants in the usual care of the current

recommended physical activity guidelines and did not discourage them from engaging in physical activity. We felt that it would be unethical to prevent participants from engaging in a physical activity, given the disease risk associated with sedentary lifestyles. In addition, it is possible that the initial consultation may have acted as a minimal intervention, and increased the awareness of physical activity in breast cancer survivors who may already have been in a higher state of 'readiness' to engage in increased levels of physical activity. Nevertheless, despite possible usual care group contamination, we found significant improvements in total physical activity in the intervention group compared to the usual care group and more participants moved to a higher physical activity category in the intervention group compared to the usual care group over the study period.

- The trial results may have been influenced by attention bias. Participants in this group received approximately 75 minutes more attention in the form of face-to-face and telephone counselling, compared to the participants in the usual care. Therefore, it is possible that the significant changes in HRQoL, in particular, found in the intervention group compared to the usual care group could in part be explained by the greater attention we gave the intervention group participants.
- Furthermore, because the outcome assessor was not blinded to the allocation of participants, the trial is at risk of assessment bias. Blinding the assessor to the allocation of participants was not possible because the primary investigator was responsible for delivering both the face-to-face and telephone counselling sessions and for performing the

outcome assessments. Assessment bias can be introduced if the outcome assessor consciously or unconsciously provides more encouragement during assessments to the participants in the intervention group than those in the usual care group, which may result in more favourable scores in the intervention group. However, every attempt was made to standardise protocols across groups and the outcome assessor was carefully trained and monitored for objective and consistent administration of protocols. In addition, assessment bias could have been introduced by the inability to blind participants to group allocation. This inability to blind participants is an inherent limitation of physical activity studies, which may bias participant responses and behaviours because of their awareness of the study purpose and desire to please the study research staff.

CHAPTER EIGHT: CONCLUSIONS

In summary, our two systematic reviews with meta-analyses revealed firstly, significant associations between higher levels of pre-diagnosis (lifetime and recent) and post-diagnosis physical activity and reduced risk of mortality, and secondly, significantly improved outcomes related to the health and quality of life of breast cancer survivors due to a physical activity intervention. Consistent with our first hypothesis, in study one we found relatively low levels of recreational physical activity in a population of breast cancer attendees and those with lower activity levels were unaware that their levels were below recommended levels of physical activity. However, contrary to our original predictions there was high awareness of the role of physical activity on the risk of breast cancer regardless of physical activity level. Therefore, the results suggest that strategies to improve awareness of how much physical activity is sufficient, and in turn the recreational physical activity levels of breast screening attendees. In study two our findings were consistent with our hypotheses, we observed lower levels of physical activity in both breast cancer patients undergoing adjuvant chemotherapy and patients post-treatment compared to breast cancer attendees. The results of the above two studies provided a rationale for an intervention aimed to promote adherence to current UK recommended physical activity guidelines in post-treatment breast cancer patients.

We tested the efficacy of a home-based physical activity intervention with an additional counselling component to increase physical activity in breast cancer survivors within a randomised controlled design setting. In agreement with our hypotheses, we found that a home-based physical

activity intervention resulted in significant favourable effects on self-reported physical activity, body mass, BMI, elements of HRQoL, TC and LDL-C concentrations, but not body fat %, TG, HDL-C, glucose, insulin or HOMA. In addition, within a random subsample of breast cancer survivors from within the main RCT, we found significant improvements in cardiorespiratory fitness in the intervention group compared to the usual care group. These results were encouraging given the highly feasible, portable and home-based nature of the intervention.

The results of each of the studies in this current project must be interpreted within the contexts of the limitations of each study. The limitations of the current project include the cross-sectional design of the first two studies, which does not provide definitive evidence for causality and directionality. The use of convenience samples increased the risk of results being influenced by recruitment bias. The homogeneity of our sample limited the generalisability of our findings to ethnic groups other than white British women. In addition, self-reported physical activity was measured as an outcome in this project, and as such our results could have been influenced by recall bias and/or social desirability bias. Furthermore, the inability to blind both the outcome assessor and trial participants exposed the RCT to assessment bias.

Future research will be needed to establish the generalisability and maintenance of physical activity in the time post-intervention. Given the potential of our intervention to reach a large population of breast cancer survivors within health and community settings, it will be important to assess whether modifications would be needed when employed in older

and perhaps less motivated breast cancer survivors. Further investigation is required to elucidate the impact of home-based physical activity interventions on glucose-insulin dynamics and confirm our beneficial effects on cardiorespiratory fitness in a sufficiently large sample of breast cancer survivors. The cost-effectiveness of home-based physical activity could be explored by comparing the costs of running this type of interventions to the possible cost-saving effects of such trials, which may include outcomes such as reduced hospital admissions and usage of health care services in the years following treatment. Perhaps most importantly, future prospective longitudinal RCTs are needed to determine the impact of physical activity and improvements in cardiorespiratory on breast cancer-related mortality, recurrence and development of CVD in breast cancer survivors.

Overall, this project highlighted the potential beneficial effects that a home-based physical activity intervention coupled with face-to-face counselling and telephone support can have on the health and well-being of breast cancer survivors, and its potential in positively impacting factors that can influence the risk of CVD and breast cancer mortality. Our findings highlight the importance of including physical activity promotion in the management and post-treatment care of breast cancer survivors. The portability and feasibility of our intervention makes it a promising intervention that could benefit a large number of breast cancer survivors in a variety of health care and community settings.

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APPENDICES

Appendix A: Tumour, Node, Metastasis (TNM) classification system, 7th Edition

(adapted from Pories, 2010)

Stage	Definition

Stage 0	• Tis – Carcinoma in situ
	  o Tis (Ductal): Intraductal carcinoma in situ
	  o Tis (LCIS): Lobular carcinoma in situ
	  o Tis (Paget): Paget disease of the nipple is not associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma (specialized human tissue located on the chest between the pectoralis muscle). Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted
	• N0 – No regional lymph node metastases
	  o pNO: No regional lymph node metastasis identified histologically
	  o pNO(i-): No regional lymph node metastases histologically, negative IHC
	  o pNo(i+): Malignant cells in regional lymph node(s) no greater than 0.2 mm
	  o pNO(mol-): No regional lymph node metastases histologically, negative molecular findings
	  o pNO(mol+): Positive molecular findings, but no regional lymph node metastases detected by histology or IHC
	• M0 – No clinical or radiographic evidence of distant metastases
	  o M0: No evidence of distant metastases

Stage IA	• T1 - Tumor ≤2 mm in greatest dimension
	  o T1mi — Tumor ≤1 mm in greatest dimension
	  o T1a — Tumor >1 mm but ≤5 mm in greatest dimension
	  o T1b — Tumor >5 mm but ≤10 mm in greatest dimension
	  o T1c — Tumor >10 mm but ≤20 mm in greatest dimension
	• N0: No regional lymph node metastases (see stage 0 for sub groupings)
	• M0: No clinical or radiographic evidence of distant metastases

Stage IB	• T0 — No evidence of primary tumour • pN1mi — Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm) • MO: cMO(i+) – No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumour cells in circulating blood, bone marrow or other non-regional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases **OR** • T1 – Tumor ≤2 mm in greatest dimension (see Stage IA for subgroups) • pN1mi — Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm) • M0 – No clinical or radiographic evidence of distant metastases

Stage IIA	• T0 — No evidence of primary tumour • N1 – Metastasis to movable ipsilateral level I, II axillary lymph nodes(s) o pN1 — Micrometastases; or metastases in 1 to 3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected (i.e. not detected by imaging studies excluding lymphoscintigraphy, or by clinical examination) o pN1mi — Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm) o pN1a — Metastases in 1 to 3 axillary lymph nodes, at least one metastasis greater than 2.0 mm o pN1b — Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected o pN1c — Metastases in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected • MO: see stage IB **OR** • T1 – Tumor ≤2 mm in greatest dimension (see Stage IA for sub groupings) • N1 – Metastasis to movable ipsilateral level I, II axillary lymph nodes(s) (see above for sub groupings) • M0 – No clinical or radiographic evidence of distant metastases **OR** • T2 **–** Tumour >20 mm but ≤50 mm in greatest dimension • N0 – No regional lymph node metastases • M0 – No clinical or radiographic evidence of distant metastases
Stage IIB	• T2 **–** Tumour >20 mm but ≤50 mm in greatest dimension • N1 – Metastasis to movable ipsilateral level I, II axillary lymph nodes(s) (see IIA for sub groupings) • M0 – No clinical or radiographic evidence of distant metastases **OR** • T3 – Tumor >50 mm in greatest dimension • N0 – No regional lymph node metastases • M0 – No clinical or radiographic evidence of distant metastases
Stage IIIA	• T0 – No evidence of primary tumour • N2 – Metastasis to ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary node metastases o pN2 – Metastases in 4-9 axillary lymph nodes; or in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases o N2a – Metastasis to ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures o pN2a – Metastases in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm) o N2b – Metastasis only in clinically detected ipsilateral internal mammary nodes and in the absence of clinically evident axillary node metastases o pN2b – Metastases in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases.

	• M0 – No clinical or radiographic evidence of distant metastases **OR** • T1 – Tumor ≤2 mm in greatest dimension (see Stage IA for sub groupings) • N2 – Metastasis to ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary node metastases (see above for sub groupings) • M0 – No clinical or radiographic evidence of distant metastases **OR** • T2 – see above for sub groupings • N2 – Metastasis to ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary node metastases (see above for sub groupings) • M0 – No clinical or radiographic evidence of distant metastases **OR** • T3 – Tumor >50 mm in greatest dimension • N1 – Metastasis to movable ipsilateral level I, II axillary lymph nodes(s) (see IIA for sub groupings) • M0 – No clinical or radiographic evidence of distant metastases • **OR** • T3 – Tumor >50 mm in greatest dimension • N2 – Metastasis to ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary node metastases (see above for sub groupings) • M0 – No clinical or radiographic evidence of distant metastases
Stage IIIB	• T4 – Tumor of any size with direct extension to the chest wall and/or the skin (ulceration or skin nodules) o T4a — Extension to chest wall, not including only pectoralis muscle adherence/invasion o T4b — Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin which do not meet the criteria for inflammatory carcinoma o T4c — Both (T4a and T4b) o T4d — Inflammatory carcinoma • N0 – No regional lymph node metastases • M0 – No clinical or radiographic evidence of distant metastases **OR** • T4 – Tumor of any size with direct extension to the chest wall and/or the skin (ulceration or skin nodules) (see above for subgroups) • N1 – Metastasis to movable ipsilateral level I, II axillary lymph nodes(s) (see IIA for sub groupings) • M0 – No clinical or radiographic evidence of distant metastases **OR** • T4 – Tumor of any size with direct extension to the chest wall and/or the skin (ulceration or skin nodules) (see above for subgroups) • N2 – Metastasis to ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary node metastases (see above for IIIA sub groupings) • M0 – No clinical or radiographic evidence of distant metastases
Stage IIIC	• Any T • N3 – Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement

	(N3a); or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases (N3b); or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement (N3c) o pN3 – Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected ipsilateral internal mammary lymph nodes in the presence of 1 or more positive level I, II axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected; or in ipsilateral supraclavicular lymph nodes o pN3a — Metastases in 10 or more axillary lymph nodes (at least one tumour deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes o pN3b – Metastases in clinically detected ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected o pN3c – Metastases in ipsilateral supraclavicular lymph nodes
Stage IV	• Any T • Any N • M1 – Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Appendix B: epidemiological systematic review; MEDLINE (via PubMed) search strategy and results

	Query	Items found
1	Search physical activity [mh]	171397
2	Search physical activ* [tiab]	52380
3	Search physical* activ* [tiab]	25569
4	Search exercise [mh]	101067
5	Search exercis* [tiab]	188821
6	Search motor activity [mh]	171397
7	Search training [tiab]	226754
8	Search sports [mh]	103589
9	Search sport* [tiab]	39560
10	Search fitness [tiab]	36630
11	Search cardiovascular [tiab]	256395
12	Search cardiorespiratory [tiab]	10078
13	Search cardio-respiratory [tiab]	1563
14	Search resistance training [mh]	2478
15	Search aerobic [tiab]	51706
16	Search walk* [tiab]	66214
17	Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)	940761
18	Search breast neoplasms [mh]	203202
19	Search cancer*	1328920
20	Search carcinom*	607735
21	Search neoplas*	2092894
22	Search malignan*	392824
23	Search tumour*	201740
24	Search tumor*	1083540
25	Search (#19 OR #20 OR #21 OR #22 OR #23 OR #24)	2924032
26	Search breast	331449
27	Search (#25 AND #26)	269050
28	Search (#17 AND #27)	7028
29	Search mortality [tiab]	432127
30	Search survival [tiab]	548430
31	Search recurrence [tiab]	170324
32	Search survivor* [tiab]	59666
33	Search death [tiab]	433653
34	Search relapse* [tiab]	100590
35	Search recurrence* [tiab]	190541
36	Search weight* [tiab]	626769
37	Search BMI [tiab]	66114
38	Search "body mass index" [tiab]	90181
39	Search fat [tiab]	163914
40	Search adipo* [tiab]	84934
41	Search overweight [tiab]	33710
42	Search obes* [tiab]	159094
43	Search prognos* [tiab]	344526
44	Search loss [tiab]	572098
45	Search gain[tiab]	143606

46	Search reduc* [tiab]	2023565
47	Search biomarkers [tiab]	53154
48	Search blood [tiab]	1324712
49	Search bio-marker* [tiab]	263
50	Search biomarker* [tiab]	78349
51	Search progress* [tiab]	674582
52	Search (#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51)	5679511
53	Search (#28 AND #52)	4516
54	Search (#28 AND #52) Filters: English	4168
55	Search (#28 AND #52) Filters: Humans; English	3632

Appendix C: details of multivariate analysis in epidemiological studies included in systematic review

1. Abrahamson et al. 2006
    - Estimates for physical activity adjusted for stage and income

2. Borugian et al. 2004
    - Estimates adjusted for age and stage at diagnosis, treatment, oestrogen receptor status, WHR, and family history of breast cancer

3. Cadmus-Bertram et al. 2011
    - All analyses adjusted for age at randomization, race, fruit and vegetable consumption, BMI at randomization, menopausal status, tumour type, tumour grade, tumour stage, anti-oestrogen use, clinical site, time from diagnosis to randomization, hot flashes, and study group

4. Chen et al. 2011
    - Estimates adjusted for date of birth, BMI at baseline, waist-to-hip ratio at baseline, menopausal status, income, education, QOL, cruciferous vegetable intake, soy protein intake, tea consumption, chemotherapy, radiotherapy, tamoxifen use, TNM status, and ER/PR status. Exercise was treated as a time-dependent variable

5. Cleveland et al. 2012
    - Estimates adjusted for age at diagnosis, BMI and menopausal status

6. Dal Maso et al. 2008
    - Estimates were adjusted for region of residence, age and year at breast cancer diagnosis, and for major tumour characteristics (i.e., TNM stage and ER/PR status)

7. Emaus et al. 2010
    - Estimates adjusted for age at diagnosis, pre-diagnostic observation time, tumor stage, region of residence (strata), year at diagnosis before and after 1995 (strata), and BMI or leisure time physical activity, respectively

8. Enger and Bernstein, 2004
    - Estimates adjusted for age, stage at diagnosis and BMI

9. Friedenreich et al. 2009
    - Recurrences: Estimates for total physical activity were adjusted for age, tumour stage, treatment (chemotherapy, hormone therapy and radiation therapy), SBR grade, BMI and other comorbidity conditions. Estimates for recreational activity, occupational activity and household activity were adjusted for other types of physical

activity, age, tumour stage, treatment (chemotherapy, hormone therapy and radiation therapy), SBR grade, BMI and other comorbidity conditions

- Breast cancer-related mortality: Estimates for total physical activity were adjusted for age, tumour stage, treatment (chemotherapy, hormone therapy and radiation therapy), SBR grade, PR status, WHR and HRT use. Estimates for recreational activity, occupational activity and household activity were adjusted for other types of physical activity, age, tumour stage, treatment (chemotherapy, hormone therapy and radiation therapy), SBR grade, PR status, WHR and HRT use
- All-cause mortality: Estimates for total physical activity were adjusted for age, tumour stage, treatment (chemotherapy, hormone therapy and radiation therapy), SBR grade, WHR, HRT use, oral contraceptive use, weight gain since age 20 and total pack-years of smoking for current and former smokers. Estimates for recreational activity, occupational activity and household activity were adjusted for other types of physical activity types, age, tumour stage, treatment (chemotherapy, hormone therapy and radiation therapy), SBR grade, WHR, HRT use, oral contraceptive use, weight gain since age 20 and total pack-years of smoking for current and former smokers. Multivariable model is adjusted for recreational physical activity, occupational physical activity, age, tumour stage, treatment (chemotherapy, hormone therapy and radiation therapy), SBR grade, WHR, HRT use, oral contraceptive use, weight gain since age 20 and total pack-years of smoking for current and former smokers

10. Hellmann et al. 2010
    - Estimates adjusted for age, disease stage, adjuvant treatment, menopausal status, parity, alcohol intake, smoking, body mass index and hormone replacement therapy

11. Holick et al. 2008
    - Estimates adjusted for age at diagnosis, stage of disease at diagnosis, state of residence at diagnosis, and interval between diagnosis and physical activity assessment. Additionally adjusted for postdiagnosis BMI, postdiagnosis menopausal status, postdiagnosis hormone therapy use, total energy intake year before enrollment in the CWLS, education level at diagnosis, family history of breast cancer at diagnosis, and initial treatment modality (radiation, chemotherapy, tamoxifen)

12. Holmes et al. 2005
    - Estimates adjusted for age (months); interval between diagnosis and physical activity assessment (28-33, 34-40, ≥41 mo); smoking status (never, current, past); body mass index (≤21, 21-22.9, 23-24.9, 25-28.9, ≥29), menopausal status and hormone therapy use (premenopausal, postmenopausal, and never use; postmenopausal and current use; postmenopausal and past use;

uncertain menopausal status; missing); age at first birth and parity (nulliparous, <25 y and 1-2 births, <25 y and ≥3 births, ≥25 y and 1-2 births, ≥25 y and ≥3 births); oral contraceptive use (never, ever, missing); energy intake (quintiles); energy-adjusted protein intake (quintiles); disease stage (I, II, III); radiation treatment (yes or no); chemotherapy (yes or no); and tamoxifen treatment (yes or no)

13. Irwin et al. 2011
    - Pre-diagnosis physical activity: Adjusted for age, ethnicity, WHI study arm, previous hormone therapy use, BMI, diabetes, alcohol, smoke, total calories, percentage calories from fat, and servings of fruit and vegetables
    - Post-diagnosis physical activity: Adjusted for age, stage, ER, PR, grade, HER2, ethnicity, WHI study arm, previous hormone therapy use, time from diagnosis to physical activity assessment, BMI, diabetes, alcohol, smoke, total calories, and percentage calories from fat, and servings of fruit and vegetables

14. Irwin et al. 2008
    - Adjusted for age, race, disease stage, initial treatment and tamoxifen use

15. Keegan et al. 2010
    - Estimates adjusted for study center (Ontario, Northern California, Australia), age of diagnosis (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, non-Hispanic Asian, other, missing), number of affected nodes (0, 1-3, 4+, missing), BMI (<25.0, 25.0-29.9, ≥30.0, missing), time since last full term pregnancy (nulliparous, <2 yrs, 2-4 yrs, ≥5 yrs, missing), ER status (negative, positive, missing), PR status (negative, positive, missing), tumor grade (1,2,3, missing), tumor size (≤20, >20, missing), and tumor type (invasive ductal, invasive lobular, other, missing)

16. Rohan et al. 1995
    - Estimates adjusted for stage and multiple breast cancer risk factors, including BMI and energy intake, but not treatment

17. Smidth et al. 2013
    - All models were adjusted for tumor size, nodal status, tumor grading, ER/PR status, radiotherapy, screening-detected tumor, HT use at diagnosis, age at diagnosis, BMI pre-diagnosis, smoking status and pack years and pre-existing angina pectoris. In addition, models for overall mortality and for other deaths were adjusted for pre-existing hypertension, previous stroke and use of insulin

18. Sternfield et al. 2009
    - Recurrence and breast cancer-related death: adjusted for age, number of positive nodes, stage, weight at 18 y, type of treatment (chemotherapy/radiation) and type of surgery (mastectomy or conserving)
    - All-cause death: adjusted for age, number of positive nodes, stage, weight at 18 y, education level and smoking status

19. West-Wright et al. 2009
    - Estimates adjusted for age (in years) and adjusted for race, BMI, total caloric intake, oestrogen receptor status, number of comorbid conditions, stage and physical activity summary variable

Appendix D: details of sub-analyses from epidemiological studies

BMI sub-analyses			
Study authors	**PA categories**	**Comparisons**	**Outcome**
Schmidt et al. (2013)	**1) Level of recreational PA (MET-h/wk):** • 0 MET-h/wk • ≥0 MET-h/wk	**a) BMI <25:** Any PA vs. No PA category	**All-cause deaths:** HR = 1.63 (1.23-2.17) **Breast cancer-related death:** HR = 1.38 (0.97-1.95)
		b) BMI ≥25: Any PA vs. No PA category	**All-cause deaths:** 1.04 (0.67, 1.61) **Breast cancer-related death:** 0.90 (0.51-1.62)
Cleveland et al. 2012 (LIBCSP)	**1) Level of recreational PA (MET-h/wk):** • 0 MET-h/wk • ≥9 MET-h/wk	**a) BMI <25:** ≥9 MET-h/wk PA (n=226/ all-cause deaths=18; n=189/breast cancer deaths=15) vs. 0 MET-h/wk (n=147/17; n=175/34)	**All-cause death:** **a)** HR = 0.45 (0.25-0.80) **Breast cancer death:** **a)** HR = 0.67 (0.32-1.40)
		b) BMI ≥25: ≥9 MET-h/wk PA (n=250/50; n=206/25) vs. 0 MET-h/wk (n=250/50; n=235/34)	**All-cause death:** **b)** HR = 0.62 (0.38-1.02) **Breast cancer death:** **b)** HR = 0.59 (0.32-1.08)
	2) Level of recreational PA (MET-h/wk): • 0 MET-h/wk >0 MET-h/wk	**a) BMI <25:** ≥0 MET-h/wk PA (n=493/all-cause deaths=39; n=416/breast cancer deaths=28) vs. 0 MET-h/wk (n=250/50; n=235/34)	**All-cause death:** **a)** HR = 0.44 (0.27-0.70) **Breast cancer death:** **a)** 0.57 (0.30-1.09)
		b) BMI ≥25: ≥9 MET-h/wk PA (n=533/69; n=452/44) vs. 0 MET-h/wk (n=250/50; n=235/34)	**All-cause death:** **b)** HR = 0.66 (0.46-0.96) **Breast cancer death:** **b)** HR = 0.63 (0.40-0.99)
Chen et al. 2011 (SBCSS)	**1) Exercise energy expenditure (MET-h/wk) in first 36 mo** • No exercise • <8.3 • ≥8.3	**a) BMI <25:** ≥8.3 (n=1,027/all-cause deaths=78; n=967/breast cancer events=87) vs. no exercise (n=1,102/113; n= 1,015/98) category	**All-cause death:** **a)** HR = 0.62 (0.45-0.85)** **Recurrence or metastasis or breast cancer-related death:** **a)** HR = 0.66 (0.47-0.94)*
		b) BMI ≥25: ≥8.3 (n=522/51; n=609/72) vs. no exercise (n=496/61; n=565/76) category	**All-cause death:** **b)** HR = 0.70 (0.46-1.05)* **Recurrence or metastasis or breast cancer-related death:** **b)** HR = 0.50 (0.38-

			0.74)
Irwin et al. 2011 (WHI)	**1) Post-diagnosis moderate-vigorous intensity PA (MET-h/wk):** • 0 • >0	**a) BMI <25:** >0 MET-h/wk (n=780/all-cause deaths=44) vs.0 MET-h/wk (n=201/20) **b) BMI 25-29.9:** >0 MET-h/wk (n=696/27) vs.0 MET-h/wk (n=305/28) **c) BMI >30:** >0 MET-h/wk (n=512/31) vs.0 MET-h/wk (n=393/32)	**All-cause death:** **a)** HR = 0.49 (0.27-0.91) **All-cause death:** **b)** HR = 0.43 (0.24-0.76) **All-cause death:** **c)** HR = 0.80 (0.45-1.41)
Keegan et al. 2010 (BCFR)	**1) Recent PA (3 y pre-diagnosis) (MET-h/wk):** • 0 (sedentary) • >0 (active)	**a) BMI <25 (n=2,220):** Sedentary (all-cause deaths=64) vs. active (all-cause deaths=234) **b) BMI ≥25 (n=1,806):** Sedentary and BMI ≥25 (67) vs. Active and BMI <25 (234) **c) BMI ≥25 (n=1,806):** Active and BMI ≥25 (213) vs. Active and BMI <25 (234)	**All-cause death:** **a)** HR = 1.46 (1.10-1.94) **All-cause death:** **b)** HR = 1.46 (1.10-1.93) **All-cause death:** **c) HR =** 1.26 (1.04-1.52)
Sternfield et al. 2009 (LACE)	**1) H/wk of moderate PA:** • <1 • >6	**a) BMI <25 (n=749):** >6 vs.<1 h/wk of moderate PA **b) BMI 25-29.9 (n=656):** >6 vs.<1 h/wk of moderate PA **c) BMI ≥ 30 (n=518):** >6 vs.<1 h/wk of moderate PA	**All-cause death:** **a)** HR = 0.38 (0.17–0.85)** **All-cause death:** **b)** HR = 0.95 (0.47–1.94) **All-cause death:** **c)** HR = 0.90 (0.38–2.16)
West-Wright et al. 2009 (CTS)	**a) Long-term combined moderate and strenuous PA (h/wk/y):** • Low PA • Intermediate PA • High PA	**a) BMI <25:** High (n=701/ all-cause deaths= 220 and breast cancer deaths=99) vs. low (n=275/191 and 100) PA category **b) BMI ≥25:** High (n=460/100 and 191) vs. low (n=227/100 and 191) recent PA category	**All-cause death:** **a)** HR = 0.83 (0.55-1.25) **Breast cancer-related death:** **a)** HR = 1.15 (0.58-2.29) **All-cause death:** **b)** HR = 0.70 (0.46-1.08) **Breast cancer-related death:** **b)** HR = 0.41 (0.23-0.74)**

Holick et al. 2008 (CWLS)	1) Total recreational PA categories based on median (MET-h/wk): • <8 • ≥8	**a) BMI <25:** ≥8 MET-h/wk (n=1,051/breast cancer deaths=15) vs.<8 MET-h/wk (n=657/11) total recreational PA quartile **b) BMI ≥25:** ≥8 MET-h/wk (n=1,157/28) vs. <8 (n=1,372/47) MET-h/wk total recreational PA quartile	**Breast cancer-related death:** **a)** HR = 0.91 (0.39-2.13) **b)** HR = 0.63 (0.39-1.02)
Irwin et al. 2008 (HEAL)	**1) PA 2 years After Diagnosis (MET-h/wk):** • 0 • >0	**a) BMI <25:** >0 MET-h/wk (n=293/all-cause deaths=19) vs.0 MET-h/wk (n=311/12) **b) BMI ≥25:** >0 MET-h/wk (n=780/all-cause deaths=44) vs.0 MET-h/wk (n=201/20)	**All-cause death:** **a)** HR = 0.74 (0.36-1.55) **All-cause death:** **b)** HR = 0.31 (0.13-0.74)
Abrahamson et al. 2006	**1) Level of PA:** • Low PA (< median) • High PA (> median)	**a) BMI <25:** High (cohort, n=401) vs. low (n=347) PA category **b) BMI ≥25:** High (n=174) vs. low (n=299) PA category	**All-cause deaths:** **a)** HR = 1.08 (0.77-1.52) **b)** HR = 0.70 (0.49-0.99)
Holmes et al. 2005 (NHS)	Physical Activity Prior to Diagnosis (MET-h/wk): • <3 MET-h/wk • ≥24 MET-h/wk	**a)BMI <25:** ≥24 MET-h/wk (n=246/breast cancer deaths= 24) vs. <3 MET-h/wk (n=437/59) **b) BMI ≥25:** ≥24 MET-h/wk (n=157/10) vs. <3 MET-h/wk (n=522/51)	**Breast cancer death:** **a)** HR = 0.61 (0.37-0.99) **b)** HR = 0.52 (0.25-1.06)**

ER-status sub-analyses			
Study authors	**PA categories**	**Comparisons**	**Outcome**
Chen et al. 2011 (SBCSS)	**1) Exercise energy expenditure (MET-h/wk) in first 36 mo** • No exercise • <8.3 • ≥8.3	**a) ER+PR+ (positive):** ≥8.3 MET-h/wk (all cause death cohort n=756/deaths=52; breast cancer events cohort n=722/events=63) vs. no exercise (n=861/70; n= 815/80) **b) ER-PR- (negative):** ≥8.3 MET-h/wk (n=416/ 45; n=393/ 48) vs. no exercise (n=478/76; n= 428/62)	**All-cause death:** a) HR = 1.32 (0.83-2.12) **Recurrence or metastasis or breast cancer-related death:** a) HR = 0.79 (0.53-1.19) **All-cause death:** b) HR = 0.40 (0.29-0.59)** **Recurrence or metastasis or breast cancer-related death:** b) HR = 0.36 (0.24-0.56)**

		c) ER+PR-/ER-PR+ (mixed): ≥8.3 MET-h/wk (n=349/28; n=321/34) vs. no exercise (n=338/31; n= 308/28)	**All-cause death:** c) HR = 0.67 (0.36–1.22) **Recurrence or metastasis or breast cancer-related death:** c) HR = 0.51 (0.27–1.00)
Irwin et al. 2011 (WHI)	**1) Post-diagnosis moderate-vigorous intensity PA (MET-h/wk):** • 0 • >0	**a) ER+:** >0 MET-h/wk (n=1,532/all-cause deaths=64) vs.0 MET-h/wk (n=688/57) **b) ER-:** >0 MET-h/wk (n=255/all-cause deaths=23) vs.0 MET-h/wk (n=123/14) **c) HER2-positive:** >0 MET-h/wk (n=202/all-cause deaths=9) vs.0 MET-h/wk (n=97/7) **d) HER2-negative:** >0 MET-h/wk (n=782/all-cause deaths=19) vs.0 MET-h/wk (n=369/21)	**All-cause death:** **a)** HR = 0.78 (0.35–1.73) **All-cause death:** **b)** HR = 0.50 (0.34–0.74) **All-cause death:** **c)** HR = 0.71 (0.16–3.11) **All-cause death:** **d)** HR = 0.37 (0.19–0.75)
Keegan et al. 2010 (BCFR)	**1) Recent PA (3 y pre-diagnosis) (MET-h/wk):** • 0 • >38.2	**a) ER+ (n=2553)** >38.2 MET-h/wk (all-cause deaths=60) vs.0 MET-h/wk (87) **b) ER- (n=881):** >38.2 MET-h/wk (44) vs.0 MET-h/wk (36)	**All-cause death:** **a)** HR = 0.67 (0.48-0.94)** **All-cause death:** **b)** HR = 1.05 (0.66-1.68)
Sternfield et al. 2009 (LACE)	**1) H/wk of moderate PA:** • <1 • >6	**a) ER+PR+ (positive) (n=1,327):** >6 vs.<1 h/wk of moderate PA **b) ER- and/or PR- (negative) (n=614):** >6 vs.<1 h/wk of moderate PA	**All-cause death:** **a)** HR = 0.59 (0.34–1.04)** **All-cause death:** **b)** HR = 0.75 (0.36–1.59)
West-Wright et al. 2009 (CTS)	**1) Long-term combined moderate and strenuous PA (h/wk/y):** • Low PA (>0.5) • High PA (≥1 of moderate or strenuous activity >3)	**a) ER+ (n=2,549):** High vs. low PA category **b) ER- (n=450):** High vs. low recent PA category	**All-cause death (n=460):** **a)** HR = 0.78 (0.56-1.11) **Breast cancer-related death (n=221):** **a)** HR = 0.46 (0.26-0.80)** **All-cause death (n=460):** **b)** HR = 0.33 (0.15-0.74)** **Breast cancer-related death**

			(n=221): **b)** HR = 0.33 (0.13-0.83)*
	2) Recent combined moderate and strenuous PA (h/wk/y): • Low PA (>0.5) • High PA (≥1 of moderate or strenuous activity >3)	**a) ER+ (n=2,549):** High vs. low PA category **b) ER- (n=450):** High vs. low recent PA category	**All-cause death (n=460):** **a)** HR = 0.89 (0.64-1.23) **Breast cancer-related death (n=221):** **a)** HR = 1.06 (0.62-1.81) **All-cause death (n=460):** **b)** HR = 0.71 (0.35-1.46) **Breast cancer-related death (n=221):** **b)** HR = 1.18 (0.51-2.74)
Irwin et al. 2008 (HEAL)	**1) PA 2 years After Diagnosis (MET-h/wk):** • 0 • >0	**a) ER+:** >0 MET-h/wk (n=393/all-cause deaths=86) vs.0 MET-h/wk (n=86/18) **b) ER-:** >0 MET-h/wk (n=120/all-cause deaths=10) vs.0 MET-h/wk (n=15/1)	**All-cause death:** **a)** HR = 1.26 (0.15 to 11.00) **All-cause death:** **b)** HR = 0.20 (0.09 to 0.46)
Holmes et al. 2005 (NHS)	**Physical Activity Prior to Diagnosis (MET-h/wk):** • <9 MET-h/wk • ≥9 MET-h/wk	**a) ER+PR+ (positive):** ≥9MET-h/wk (n=609/breast cancer deaths= 38) vs. <9 MET-h/wk (n=955/99) **b) ER-PR- (negative):** ≥9 MET-h/wk (n=149/13) vs. <9 MET-h/wk (n=272/27)	**Breast cancer death:** **a)** HR = 0.50 (0.34-0.74) **b)** HR = 0.91 (0.43-1.96)

Stage sub-analyses			
Study authors	**PA categories**	**Comparisons**	**Outcome**
Chen et al. 2011 (SBCSS)	**1) Exercise energy expenditure (MET-h/wk) in first 36 mo** • No exercise • <8.3 • ≥8.3	**a) TNM I-IIa:** ≥8.3 MET-h/wk (all cause death cohort n=1,096/deaths=55; breast cancer events cohort n=1,048/events=71) vs. no exercise (n=1,123/67; n= 1,044/69) **b) TNM IIb-III:** ≥8.3 MET-h/wk (n=382/66; n=351/ 68) vs. no exercise	**All-cause death:** a) HR = 0.89 (0.59–1.36) **Recurrence or metastasis or breast cancer-related death:** a) HR = 0.62 (0.41–0.92) **All-cause death:** b) HR = 0.52 (0.37–0.72)**

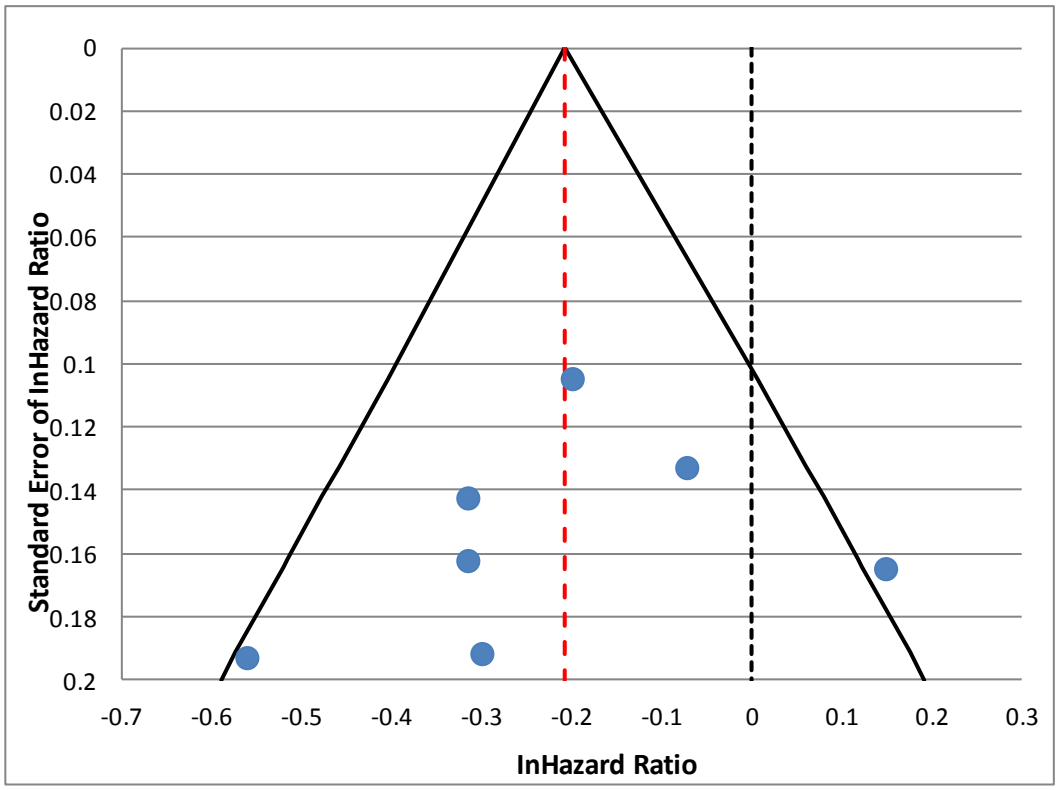
		(n=505/110; n= 461/102)	**Recurrence or metastasis or breast cancer-related death:** b) HR = 0.45 (0.32–0.64)**
Irwin et al. 2011 (WHI)	**1) Post-diagnosis moderate-vigorous intensity PA (MET-h/wk):** • 0 • >0	**a) Stage I:** >0 MET-h/wk (n=1,535/all-cause deaths=60) vs.0 MET-h/wk (n=654/43) **b) Stage II-IIIa:** >0 MET-h/wk (n=423/all-cause deaths=36) vs.0 MET-h/wk (n=234/33)	**All-cause death:** **a)** HR = 0.65 (0.42–0.99) **All-cause death:** **b)** HR = 0.46 (0.27–0.78)
West-Wright et al. 2009 (CTS)	**1) Long-term combined moderate and strenuous PA (h/wk/y):** • Low PA (>0.5) • High PA (≥1 of moderate or strenuous activity >3)	**a) Localised (n=2,437):** High vs. low PA category **b) Nonlocalised (n=1,074):** High vs. low PA category	**All-cause death (n=460):** **a)** HR = 0.75 (0.51-1.09) **Breast cancer-related death (n=221):** **a)** HR = 0.35 (0.17-0.73)** **All-cause death (n=460):** **b)** HR = 0.66 (0.42-1.05) **Breast cancer-related death (n=221):** **b)** HR = 0.57 (0.34-0.96)*
	2) Recent combined moderate and strenuous PA (h/wk/y): • Low PA (>0.5) • High PA (≥1 of moderate or strenuous activity >3)	**a) Localised (n=2,437):** High vs. low PA category **b) Nonlocalised (n=1,074):** High vs. low PA category	**All-cause death (n=460):** **a)** HR = 0.75 (0.53-1.08) **Breast cancer-related death (n=221):** **a)** HR = 0.94 (0.48-1.83) **All-cause death (n=460):** **b)** HR = 0.84 (0.55-1.29) **Breast cancer-related death (n=221):** **b)** HR = 1.09 (0.67-1.79)
Holick et al. 2008 (CWLS)	**1) Total recreational PA categories based on median (MET-h/wk):**	**a) Local stage:** ≥8 MET-h/wk (n=1,645/breast cancer deaths=20) vs.<8 MET-h/wk	**Breast cancer-related death:** **a)** HR = 0.81 (0.44-1.51)

	• <8 • ≥8	(n=1,610/24) total recreational PA **b) Regional stage:** ≥8 MET-h/wk (n=660/ 26) vs.<8 MET-h/wk (n=567/39) total recreational PA	**b)** HR = 0.56 (0.34-0.94)
Irwin et al. 2008 (HEAL)	**1) PA 2 years After Diagnosis (MET-h/wk):** • 0 • >0	**a) Stage I:** >0 MET-h/wk (n=407/all-cause deaths=19) vs.0 MET-h/wk (n=85/13) **b) Stage II-IIIa:** >0 MET-h/wk (n=167/all-cause deaths=12) vs.0 MET-h/wk (n=29/9)	**All-cause death:** **a)** HR = 0.53 (0.23 to 1.20) **All-cause death:** **b)** HR = 0.65 (0.42–0.99)
Holmes et al. 2005 (NHS)	**Physical Activity Prior to Diagnosis (MET-h/wk):** • <9 MET-h/wk • ≥9 MET-h/wk	**a) Stage I:** ≥9MET-h/wk (n=685/breast cancer deaths=26) vs. <9 MET-h/wk (n=1,083/52) **b) Stage II:** ≥9MET-h/wk (n=405/breast cancer deaths=45) vs. <9 MET-h/wk (n=609/94) **c) Stage III:** ≥9MET-h/wk (n=76/breast cancer deaths=15) vs. <9 MET-h/wk (n=129/48)	**Breast cancer death:** **a)** HR = 0.67 (0.41-1.09) **b)** HR = 0.62 (0.43-0.90) **c)** HR = 0.36 (0.19-0.71)

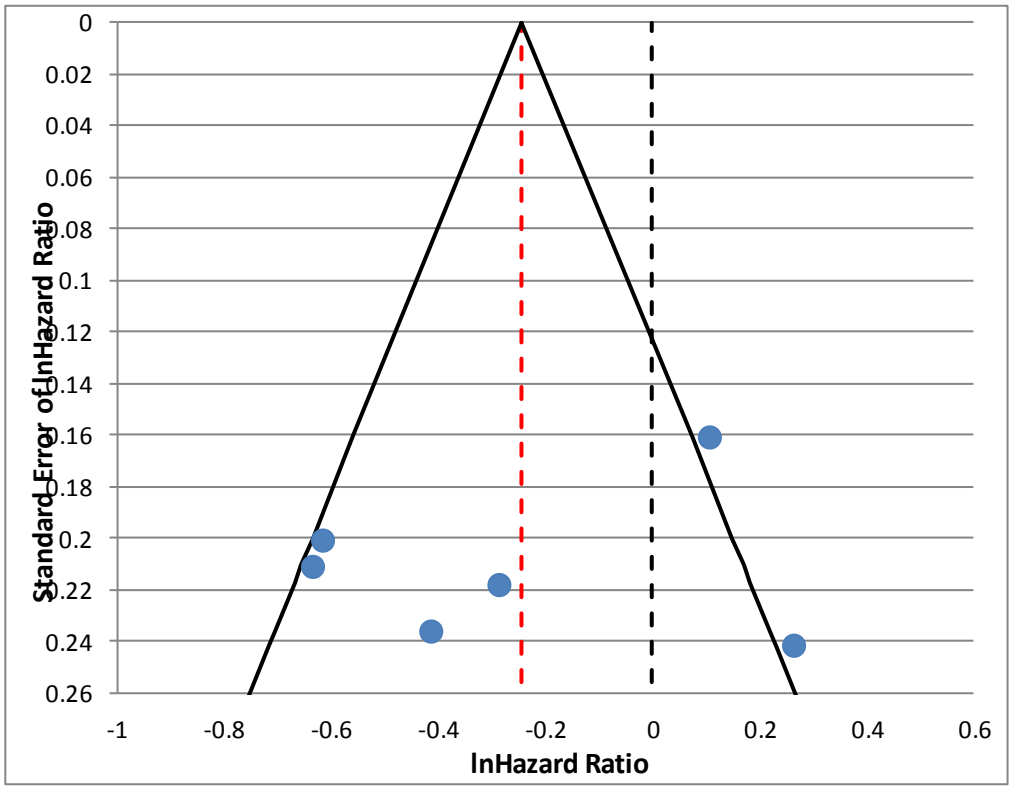
Menopause status sub-analyses			
Study authors	**PA categories**	**Comparisons**	**Outcome**
Chen et al. 2011 (SBCSS)	**1) Exercise energy expenditure (MET-h/wk) in first 36 mo** • No exercise • <8.3 • ≥8.3	**a) Premenopause:** ≥8.3 MET-h/wk (all cause death cohort n=760/deaths=61; breast cancer events cohort n=715/events=72) vs. no exercise (n=835/76; n= 773/81) **b) Postmenopause:** ≥8.3 MET-h/wk (n=789/68; n=748/ 76) vs. no exercise (n=876/109; n= 807/93)	**All-cause death:** a) HR = 0.86 (0.58–1.26) **Recurrence or metastasis or breast cancer-related death:** a) HR = 0.69 (0.47–1.00) **All-cause death:** b) HR = 0.55 (0.40–0.77)** **Recurrence or metastasis or breast cancer-related death:** b) HR = 0.52 (0.36–0.74)**

Emaus et al. 2010	**1) Pre-diagnosis recreational PA** • Sedentary • Regular exercise	**a) Premenopause (< 55 y, includes perimenopause):** Regular exercise (n = 51/17) vs. sedentary category (n = 106/39) **a) Postmenopause (≥ 55 y):** Regular exercise (n = 86/22) vs. sedentary category (n = 165/57)	**All-cause deaths:** HR = 0.96 (0.54-1.72) **Breast cancer-related death:** HR = 0.96 (0.52-1.80) **All-cause deaths:** 0.60 (0.36-0.99) **Breast cancer-related death:** 0.57 (0.31-1.04)
Hollick et al. 2008 (CWLS)	**1) Total recreational PA categories based on median (MET-h/wk):** • <8 • ≥8	**a) Age at diagnosis ≤59 y:** ≥8 MET-h/wk (n=1,288/breast cancer deaths=26) vs.<8 MET-h/wk (n=917/35) total recreational PA **b) Age at diagnosis >59 y:** ≥8 MET-h/wk (n=1,017/20) vs.<8 MET-h/wk (n=1,260/28) total recreational PA	**Breast cancer-related death:** **a)** HR = 0.53 (0.31-0.89) **b)** HR = 0.85 (0.47-1.54)
Irwin et al. 2008 (HEAL)	**1) PA 2 years After Diagnosis (MET-h/wk):** • 0 • >0	**a) Age at diagnosis <55 y:** >0 MET-h/wk (n=294/all-cause deaths=10) vs.0 MET-h/wk (n=32/5) **b) Age at diagnosis ≥55 y:** >0 MET-h/wk (n=280/all-cause deaths=21) vs.0 MET-h/wk (n=82/17)	**All-cause death:** **a)** HR = 0.18 (0.05 to 0.60) **All-cause death:** **b)** HR = 0.29 (0.14–0.60)
Holmes et al. 2005 (NHS)	**Physical Activity Prior to Diagnosis (MET-h/wk):** • <9 MET-h/wk • ≥9 MET-h/wk	**a) Premenopause:** ≥9MET-h/wk (n=242/breast cancer deaths=19) vs. <9 MET-h/wk (n=289/39) **b) Postmenopause:** ≥9 MET-h/wk (n=836/breast cancer deaths=66) vs. <9 MET-h/wk (n=1,406/140)	**Breast cancer death:** **a)** HR = 0.58 (0.32-1.04) **b)** HR = 0.73 (0.54-0.98)
Rohan et al. 1995	**1) Total recreational PA (kcal/min)** • 0 • >4,000	**a) Premenopausal:** >4,000 (n=33/breast cancer deaths=10) vs. 0 kcal/min (n=32/10) **b) Postmenopausal:** >4,000 (n=51/breast cancer death=12) vs. 0 kcal/min (n=90/29)	**Breast cancer death:** **a) HR =** 1.38 (0.45-4.26) **b) HR = 0.72 (0.29-**1.81)

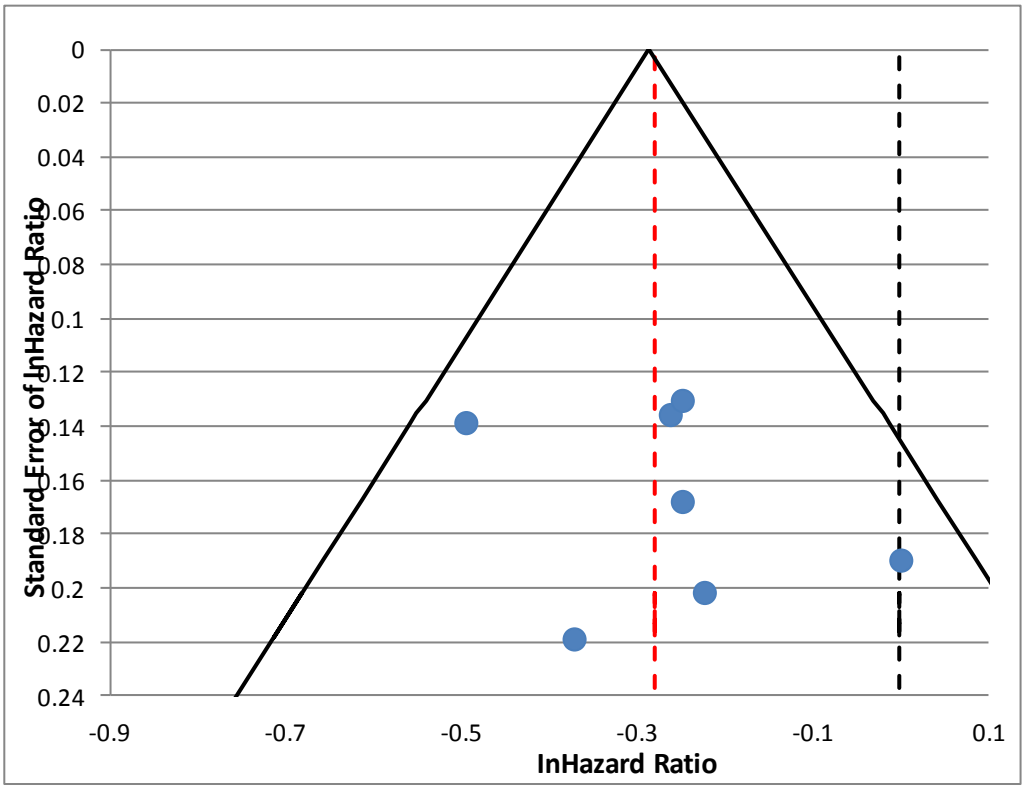
Appendix E: funnel plots from epidemiological studies meta-analysis



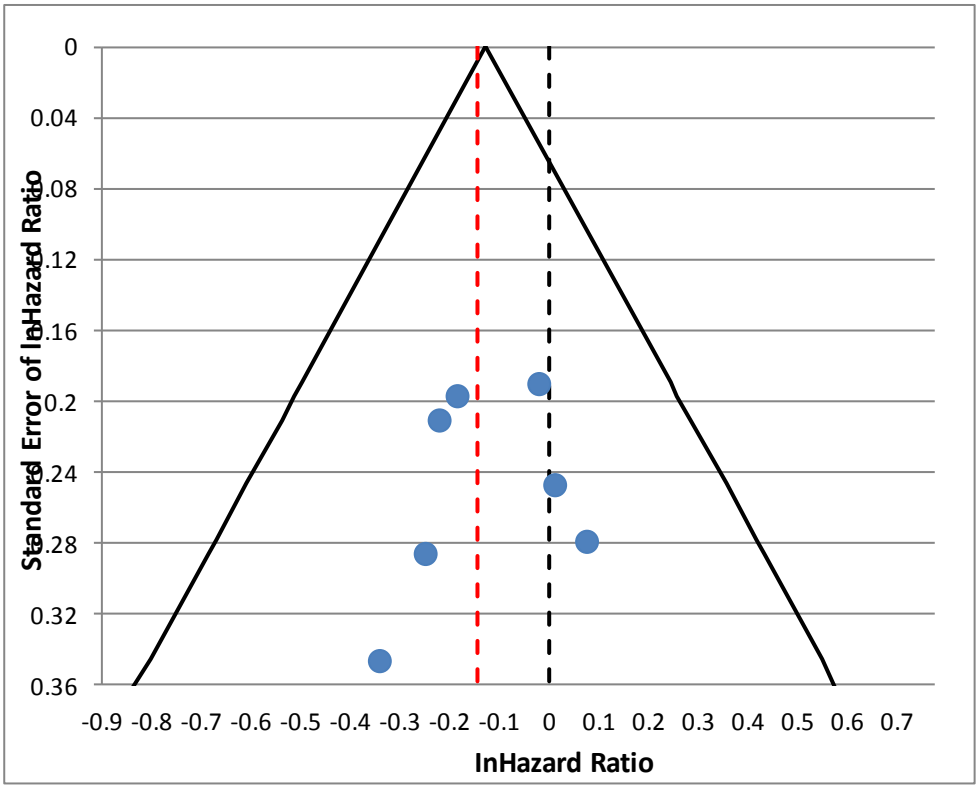
Lifetime pre-diagnosis recreational physical activity and all-cause death and funnel plot



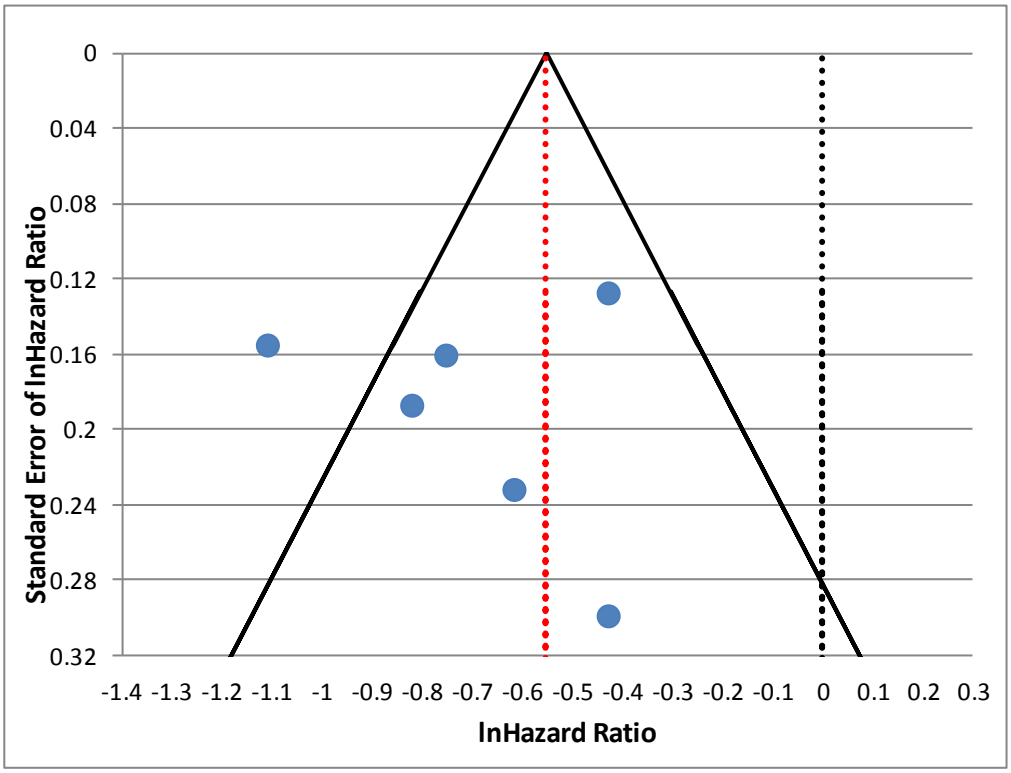
Lifetime pre-diagnosis recreational physical activity and breast cancer-related death funnel plot



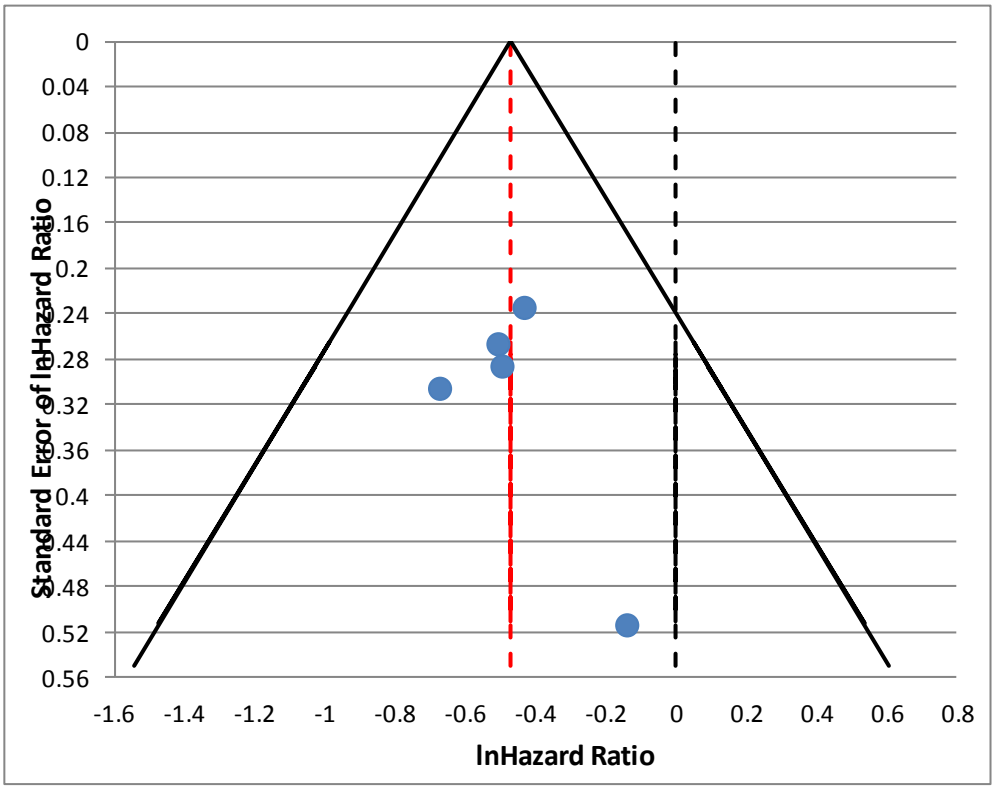
Recent pre-diagnosis recreational physical activity and all-cause death funnel plot



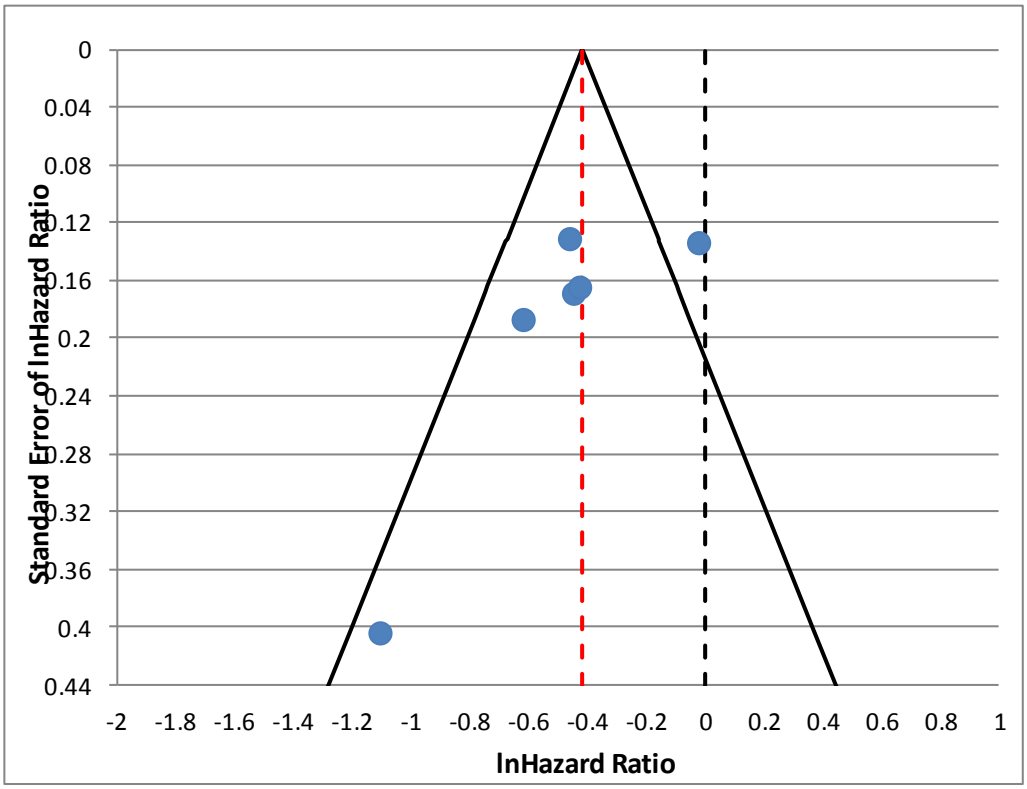
Recent pre-diagnosis recreational physical activity and breast cancer-related death funnel plot



Post-diagnosis recreational physical activity and all-cause death funnel plot



Post-diagnosis recreational physical activity and breast cancer-related death funnel plot



Meeting recommended physical activity guidelines post-diagnosis and all-cause death funnel plot

Appendix F: search strategy and results of the systematic review of physical activity interventions in breast cancer patients after adjuvant therapy

1. Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2012, Issue 10):

#1. MeSH descriptor: [Breast Neoplasms] explode all trees	7465
#2. breast near cancer*	13765
#3. breast near neoplasm*	7805
#4. breast near carcinoma*	1421
#5. breast near tumour*	323
#6. breast near tumor*	565
#7. Masectom*	1
#8. Axillary near dissection*	431
#9. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8	15054
#10. MeSH descriptor: [Exercise] explode all trees	11452
#11. Enter terms for search Exercis*	37884
#12. MeSH descriptor: [Motor Activity] explode all trees	13162
#13. MeSH descriptor: [Sports] explode all trees	7301
#14. Sport*	10268
#15. MeSH descriptor: [Resistance Training] explode all trees	697
#16. training	29927
#17. fitness	3919
#18. Physical near activit*	6223
#19. Activ*	98579
#20. MeSH descriptor: [Behavior] explode all trees	41168
#21. Behaviour*	12733
#22. Behavior*	35381
#23. #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22	189077
#24. #9 and #23	2964

2. MEDLINE search strategy and results (1966- 11th Oct 2012)

#1. Breast neoplasm*	195998
#2. Breast cancer*	156009
#3. Breast tumour*	2613
#4. Breast tumor*	12073
#5. Masectomy	7
#6. Masectom*	7
#7. Axillary dissection*	2234
#8. Breast carcinoma*	23293
#9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	235994
#10. Exercise	245000
#11. Exercis*	238638
#12. Motor control	59781
#13. Sports	129732
#14. Sport*	82040
#15. Resistance training	9172
#16. Training	969792
#17. Fitness	47194
#18. Physical activity	269678
#19. Physical activ*	229752
#20. Activ*	1097721
#21. Behaviour	176148

#22. Behavior 862178
#23. #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 3252048
#24. #9 AND #23 31415
#25. Randomised [tiab] 53641
#26. Randomized controlled trial* [pt] 331679
#27. Controlled clinical trial [PT] 84496
#28. Randomised controlled trial* 16591
#29. Randomized [tiab] 272572
#30. Randomly [tiab] 186951
#31. Drug therapy [sh] 1547923
#32. Trial [tiab] 313924
#33. Groups [tiab] 1230493
#34. Placebo [tiab] 143615
#35. #25 OR #26 OR #27 OR #28 OR #29 OR #31 OR #32 OR #33 OR #34 3057911
#36. #24 AND #35 7688
#37. #24 AND #36 Filters: Humans 7206

3. Embase (1980 to 2012 Week 40), Global Health (1973 to Sept 2012) HMIC Health Management Information Consortium (1979 to Sept 2012) and PsycINFO search strategy and results

1. exp Breast Neoplasms 313324
2. (breast adj6 cancer$).mp. 469398
3. (breast adj6 neoplasm$).mp. 28150
4. (breast adj6 carcinoma$).mp. 103000
5. (breast adj6 tumour$).mp. 17652
6. (breast adj6 tumor$).mp. 147389
7. Masectom$.mp. 15
8. (Axillary adj6 dissection*).mp. 11811
9. Searches 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 543869
10. exp Exercise/ 207246
11. Exercis$.mp. 688418
12. exp Motor control/ 18944
13. exp Sports/ 97571
14. Sport$.mp. 280439
15. exp Resistance training/ 3072
16. Training.mp. 1002911
17. Fitness.mp. 126469
18. (Physical adj6 activit$).mp. 251625
19. Activ$.mp. 6840274
20. exp Behavior/ 2884760
21. Behavio?r$.mp. 2813736
22. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 11199449
23. 9 and 22 221520

24. random:.tw.
    1997422
25. clinical trial:.mp.
    1441746
26. exp health care quality/
    1739857
27. 24 or 25 or 26
    4318113
28. limit 27 to human 30042

Results:

Embase (1980 to 2012 Week 40)

(29089)

Global Health (1973 to September 2012) (391)

HMIC Health Management Information

Consortium (1979 to September 2012) (51)
PsycINFO (1967 to October Week 2 2012) (511)

4. CINAHL search strategy and results:

1. Randomized controlled trial OR randomised controlled trial OR controlled clinical trial OR Clinical trial OR random OR health care quality OR Trial 169826
2. Exercise OR motor control OR sport OR resistance training OR Fitness OR Physical activity OR behaviour OR Behavior OR Training 305387
3. Breast cancer OR Breast neoplasms OR breast tumour OR breast tumor OR mastectomy OR axillary dissection OR breast carcinoma 44708
4. 2 AND 3 3137
5. 1 AND 4 425

5. PeDRO search strategy and results:

1. Cancer (clinical trials only) 536
2. Breast cancer 377
3. Breast neoplasms 1
4. Breast carcinoma 7
5. Breast tumor 15
6. Breast tumour 3
7. Mastectomy 0
8. Mastectomies 0
9. Axillary dissection 0

Total: 939

6. SPORTdiscus search strategy and results:

1. Randomized controlled trial OR randomised controlled trial OR controlled clinical trial OR Clinical trial OR random OR health care quality OR Trial 17503
2. Exercise OR motor control OR sport OR resistance training OR Fitness OR Physical activity OR behaviour OR Behavior OR Training 923600
3. Breast cancer OR Breast neoplasms OR breast tumour OR breast tumor OR mastectomy OR axillary dissection OR breast carcinoma 3180

4. 2 AND 3 1040
5. 1 AND 4 74

7. OPENGrey

1. Breast cancer 389
2. Breast Neoplasms 5
3. Breast carcinoma 47
4. Breast tumor 11
5. Breast tumour 22
6. Mastectomy 0
7. Mastectomies 0
8. Axillary dissection 0

Total: 474

8. ProQuest (Dissertations and Theses and Conference Papers and Proceedings Index, 1861 to October 2012)

1. Breast cancer AND exercise 477
2. Breast cancer AND physical activity OR fitness 636
3. Breast cancer AND sport OR resistance training 355
4. Breast cancer AND behaviour OR behavior 716
5. Breast neoplasms AND exercise 23
6. Breast neoplasms AND physical activity OR fitness 28
7. Breast neoplasms AND sport OR resistance training 13
8. Breast neoplasms AND behaviour OR behavior 34
9. Breast carcinoma AND exercise OR physical activity 79
10. Breast carcinoma AND sport OR fitness 35
11. Breast carcinoma AND behaviour OR behavior 83
12. Breast carcinoma AND resistance training 22
13. Breast tumor AND exercise OR physical activity 139
14. Breast tumor AND sport OR fitness 58
15. Breast tumor AND behaviour OR behavior 135
16. Breast tumor AND resistance training 38
17. Breast tumour AND exercise OR physical activity 139
18. Breast tumour AND sport OR fitness 58
19. Breast tumour AND behaviour OR behaviour 135
20. Breast tumour AND resistance training 38
21. Mastectomy 2
22. Axillary dissection 8

Total: 3,251

9. Web of knowledge search strategy and results: (Science Citation Index Expanded, 1970 to October 2012; Social Sciences Citation Index, 1970 to October 2012; Arts and Humanities Citation Index, 1975 to October 2012; and Conference Proceedings Citation Index of Science and Social Science, 1990 to October 2012)

1 TS=randomised controlled trial
196,124
2 TS=randomized controlled trial
196,124
3 TS=controlled clinical trial
136,465
4 TS=clinical trial
335,383

# 5	TS=random*	
	981,749	
# 6	TS=trial	
	850,451	
# 7	#6 OR #5 OR #4 OR #3 OR #2 OR #1	
	1,492,151	
# 8	TS=breast neoplasms	12,537
# 9	TS=breast cancer	
	293,160	
# 10	TS=breast carcinomas	92,647
# 11	TS=(breast Near Cancer)	
	277,285	
# 12	TS=breast tumour	
	123,180	
# 13	TS=breast tumor	
	123,180	
# 14	TS=mastectomy	3
# 15	#14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8	
	316,601	
# 16	TS=exercise	
	241,089	
# 17	TS=physical activity	
	119,741	
# 18	TS=resistance training	11,622
# 19	TS=activit*	
	2,426,049	
# 20	TS=fitness	65,538
# 21	TS=training	
	415,379	
# 22	TS=motor control	89,644
# 23	TS=sport*	65,588
# 24	#23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16	
	3,116,690	
# 25	#24 AND #15	51,596
# 26	#25 AND #7	8,287

Appendix G: Details of excluded studies from systematic review of physical activity interventions

Trial	Reason
Andersen 2006	This study was excluded as it was not an RCT or a CTT
Banasik 2009	This study was excluded because it contained patients with metastatic disease
Basen-Engquist 2006	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Bennet 2007	This study was excluded because breast cancer population was not analysed separately
Bloom 2008	This study was excluded because it contained patients with metastatic disease
Burnham 2002	This study was excluded because breast cancer population was not analysed separately
Cadmus Bertram 2011	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Campbell 2012	This study was excluded as it was not an RCT or a CCT
Carson 2009	This study was excluded because it contained patients with metastatic disease
Carter 2012	This study was excluded because it did not compare an exercise with no exercise or control or usual care
Cheema 2006	This study was excluded because it did not compare an exercise with no exercise or control or usual care
Classen 2008	This study was excluded because exercise was not promoted or measured
Cohen 2010	This study was excluded because all patients were pre-treatment
Courneya 2003	This study was excluded because it did not include a separate analysis of breast cancer patients
Crane-Okada 2012	This study was excluded because the intervention did not involve physical activity
Cruess 2000	This study was excluded because exercise was not promoted or measured
Culos Reed 2006	This study was excluded because it contained multiple cancers
Cunningham 1998	This study was excluded because groups contained participants with metastatic disease
D'Attilio 2007	This study was excluded because it lacked a non-exercising comparison group
Danhauer 2009	This study was excluded because it included breast and ovarian cancer patients and breast cancer population was not analysed separately
Damush 2006	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
De Backer 2007	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Demark-Wahnefried 2006	This study was excluded because it did not include a separate analysis of breast cancer patients
Dimeo 2008	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Djuric 2002	This study was excluded because it included a combined exercise and diet intervention where the effects of exercise could not be isolated.
Eyigor 2010	This study was excluded because it included the comparison group were recommended walking exercise
Galantino 2012	This was excluded because it was a qualitative study
Gielissen 2012	This study was excluded because breast cancer population was not analysed separately

Gordon 2005	This study was excluded because it included exercises restricted to stretching and local muscular endurance (i.e. training of shoulders)
Graves 2005	This study was excluded because exercise was not promoted or measured
Haas 2001	This study was excluded as it was not an RCT or a CTT
Hanna 2008	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Hayes 2009	This study was excluded because it included a therapeutic exercise regimen that addressed only specific impairments related to the shoulder and arm
Haykowsky 2009	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Headley 2004	This study was excluded because groups contained participants with metastatic disease
Hislop 2006	This study was excluded because exercise was not promoted or measured
Hojan 2011	This study was excluded because it did not contain a comparison group
Hong 2007	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Hsieh 2008	This study was excluded because it included participants undergoing chemotherapy and radiotherapy
Hunt-Shank 2006	This study was excluded because it did not contain a comparison group
Ibfelt 2011	This study was excluded because breast cancer population was not analysed separately
Ingram 2001	This study was excluded because it did not contain a comparison group
Johnsson 2011	This study was excluded because it did not contain a comparison group
Jonsson 2009	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Kilbreath 2006	This study was excluded because it included exercises restricted to stretching and local muscular endurance (i.e. training of shoulders)
Kilgour 2008	This study was excluded because it included exercises restricted to stretching and local muscular endurance (i.e. training of shoulders)
Kilka 2008 and 2009	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Kim Soo 2011	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Kovacic 2011	
LaStayo 2011	This study was excluded because breast cancer population was not analysed separately
Loprinzi 2012	This study was excluded because breast cancer population was not analysed separately
Luctkar Faude 2007	This study was excluded because breast cancer population was not analysed separately
May 2008 and 2009	This study was excluded because breast cancer population was not analysed separately
McClure 2010	This study was excluded because it included exercises restricted to stretching and local muscular endurance (i.e. training of shoulders)
McGuire 2008	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care

McKenzie 2003	This study was excluded because it included only quality of life assessment and outcomes related to only specific impairments related to the shoulder and arm
McTiernan 1998	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Moadel 2007	This study was excluded because it included patients undergoing adjuvant cancer therapy (chemotherapy)
Mustian 2009	This study was excluded because it included participants undergoing radiotherapy
Noble 2012	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Oh 2010 and 2012	This study was excluded because breast cancer population was not analysed separately
Oldervoll 2011	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Pinto 2008	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Portela 2008	This study was excluded because groups contained participants with metastatic disease
Rabin 2006	This study was excluded because it lacked a non-exercising comparison group
Rabin 2009	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Sandel 2005	This study was excluded because it included patients undergoing adjuvant cancer therapy (chemotherapy and radiotherapy)
Schmidt 2012	This study was excluded because it lacked a non-exercising comparison group
Schmitz 2010	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care (PAL pilot)
Schneider 2007	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Schwartz 1999	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Segar 1998	This study was excluded because it included patients undergoing adjuvant cancer therapy (chemotherapy and radiotherapy)
Sherman 2010	This study was excluded because the intervention group contained participants with metastatic disease
Speed-Andrews 2010	This study was excluded because it did not contain a comparison group
Sprod 2005	This study was excluded because it lacked a non-exercising comparison group
Stan 2012	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Stevinson 2006	This study was excluded because breast cancer population was not analysed separately
Stolley 2009	This study was excluded because it lacked a comparison group
Szczepanska 2010	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Tang 2010	This study was excluded because breast cancer population was not analysed separately
Thorsen 2005	This study was excluded because breast cancer population was not analysed separately

Tidhar 2010	This study was excluded because it involved therapeutic exercise regimens addressing only specific impairments related to the shoulder, arm or both.
Turner 2004	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Twiss 2009	This study was excluded because it included and medication combined group compared to a comparison group on medication exercise
Ulger 2010	This study was excluded because it did not contain a comparison group
Van Puymbroeck 2011	This study was excluded because it lacked a non-exercising comparison group
Van Weert 2005	This study was excluded because breast cancer population was not analysed separately
Vos 2006	Trial did not promote physical activity as a part of the intervention and/or measure physical activity as an outcome
Waltman 2003	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Wilson 2006	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Wong 2012	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Wu 2008	This study was excluded as it did not compare an exercise with no exercise, another intervention, or usual care
Yuen 2007	This study was excluded because it included two patients undergoing adjuvant cancer therapy (chemotherapy or radiotherapy) in each of the two intervention groups and one patient in the control group

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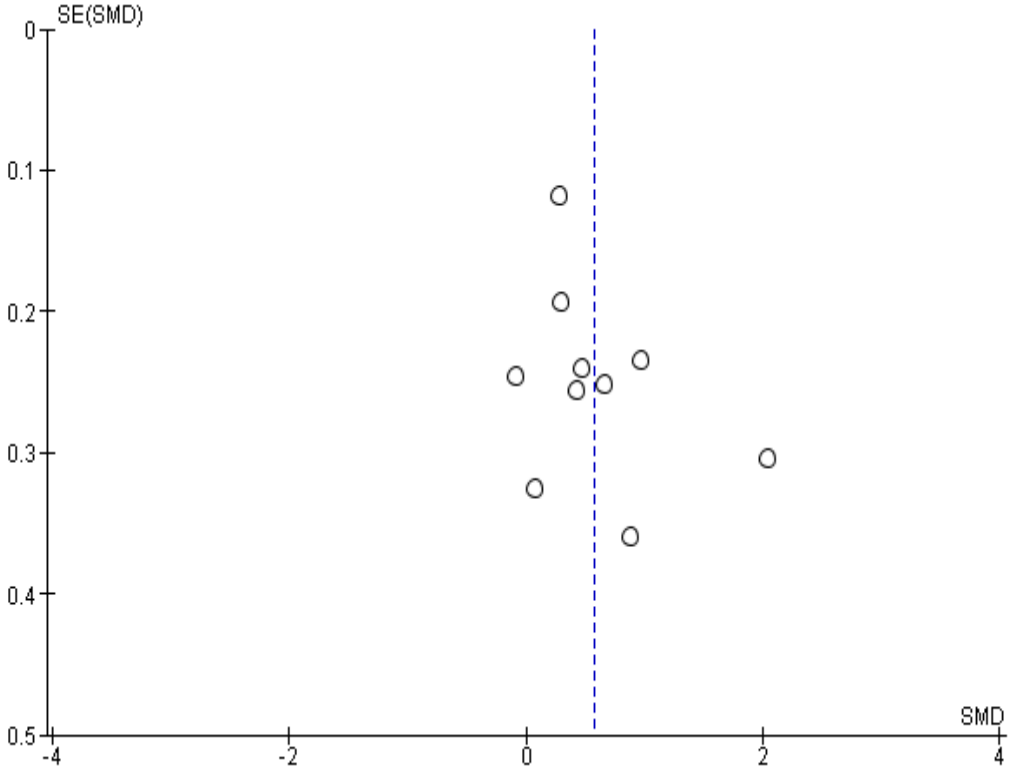
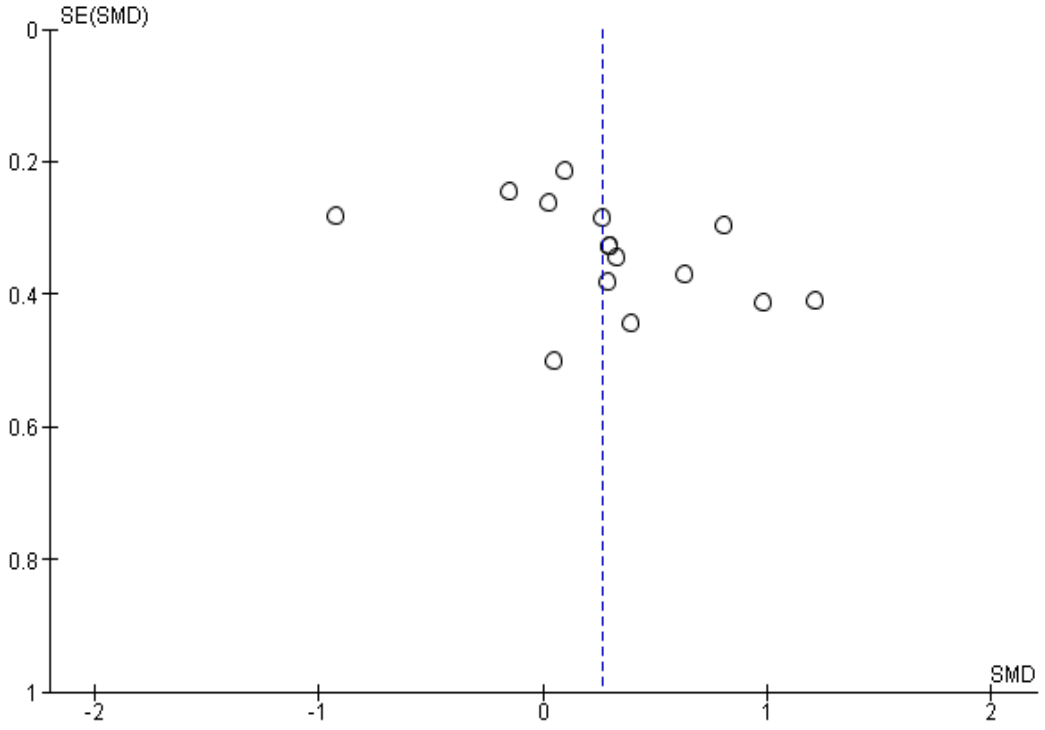
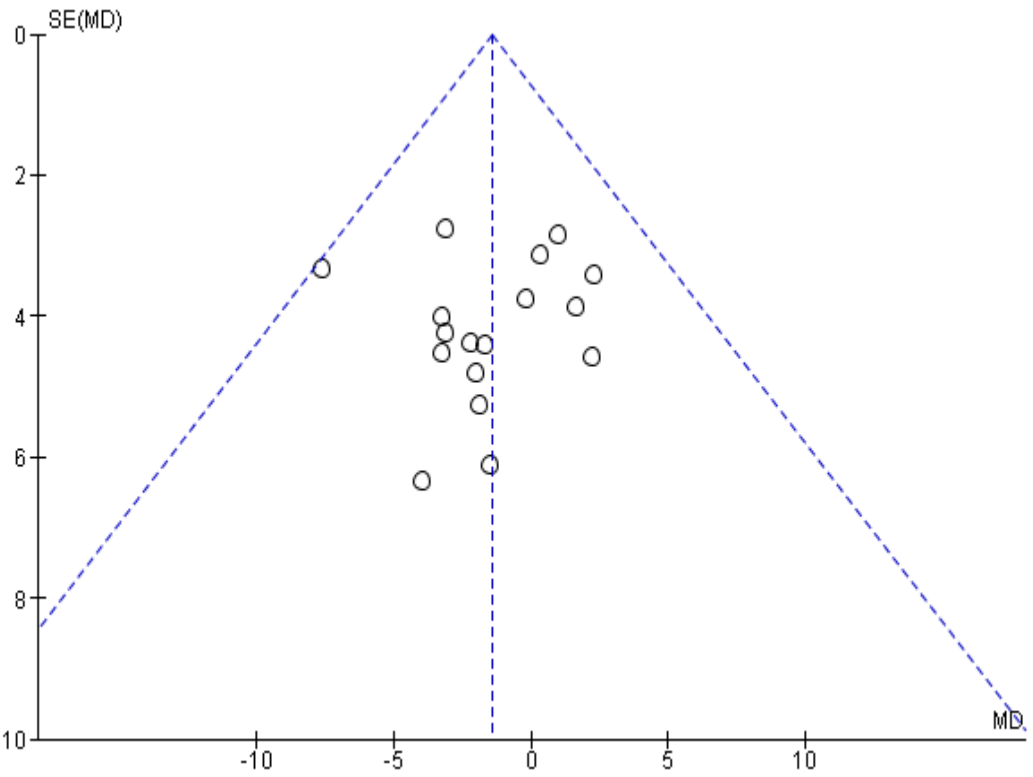
Appendix H: Funnel plots from RCT systematic review



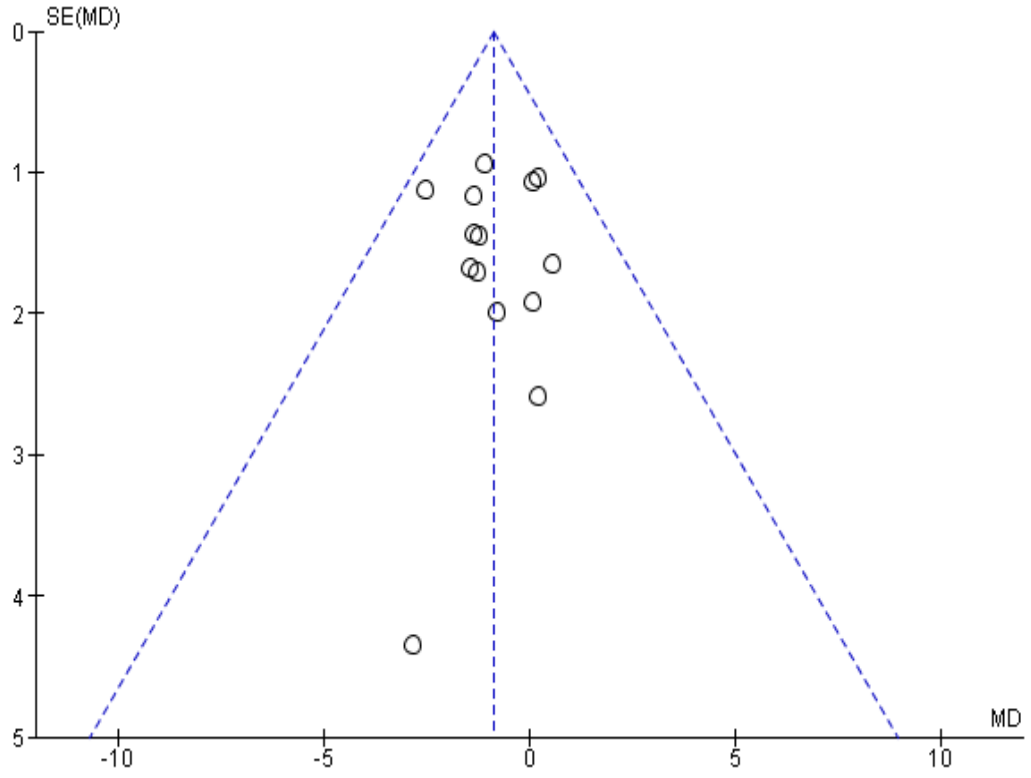
Funnel Plot: Physical activity



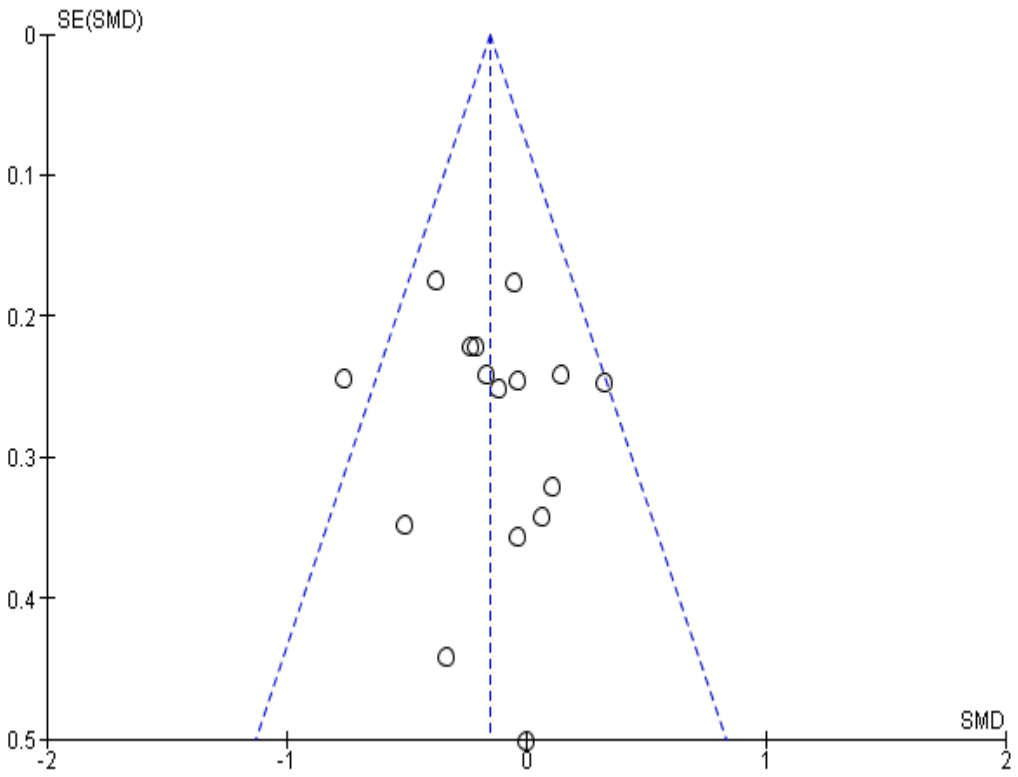
Funnel plot: Cardiorespiratory fitness



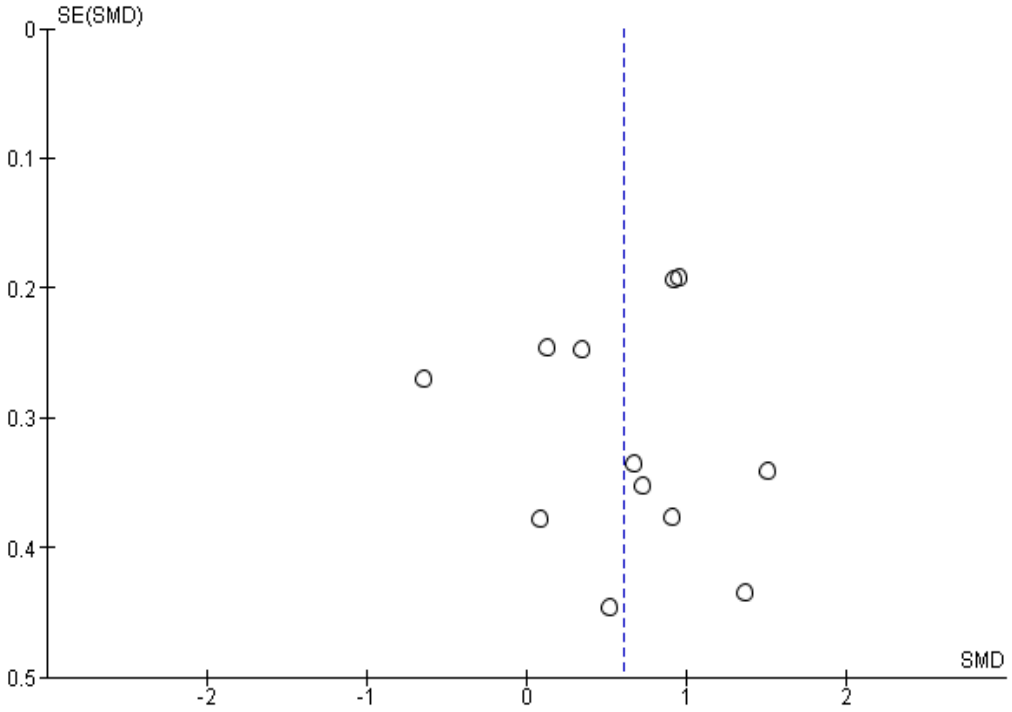
Funnel plot: Body mass



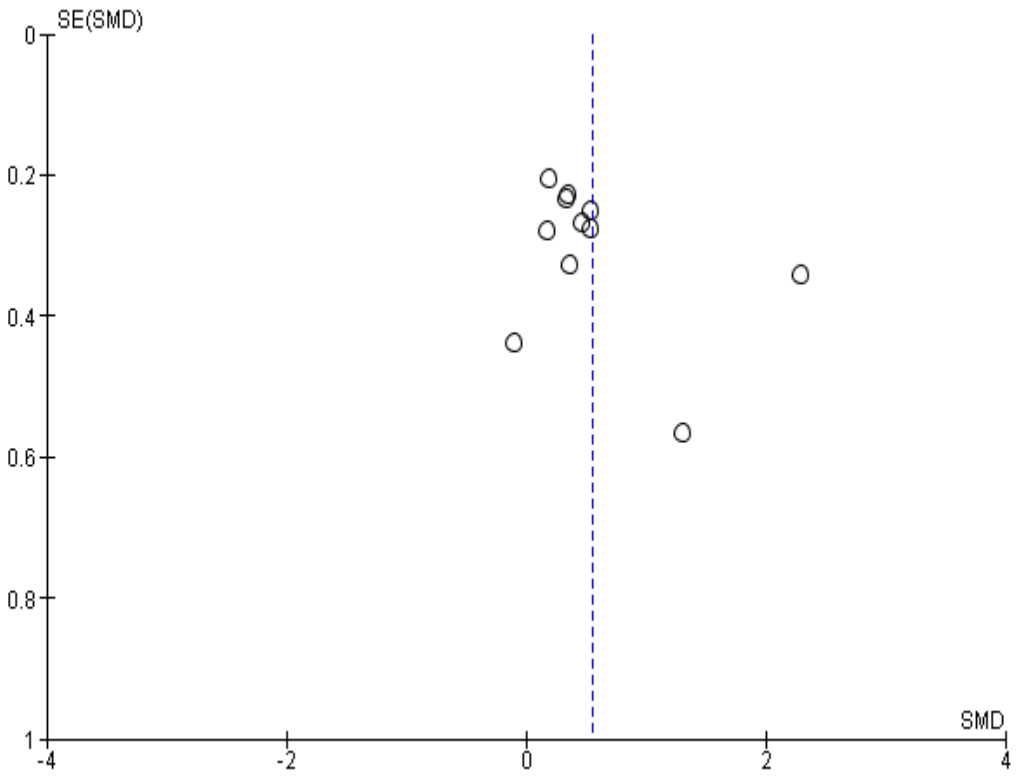
Funnel plot: Body mass index



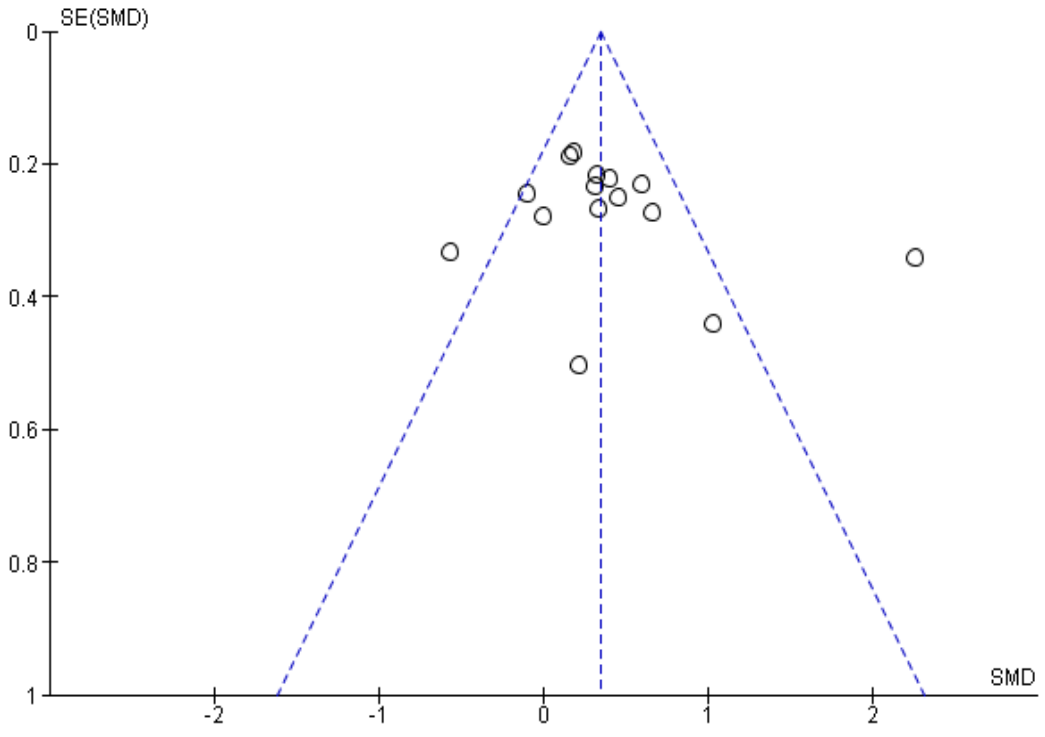
Funnel plot: Body fat percentage



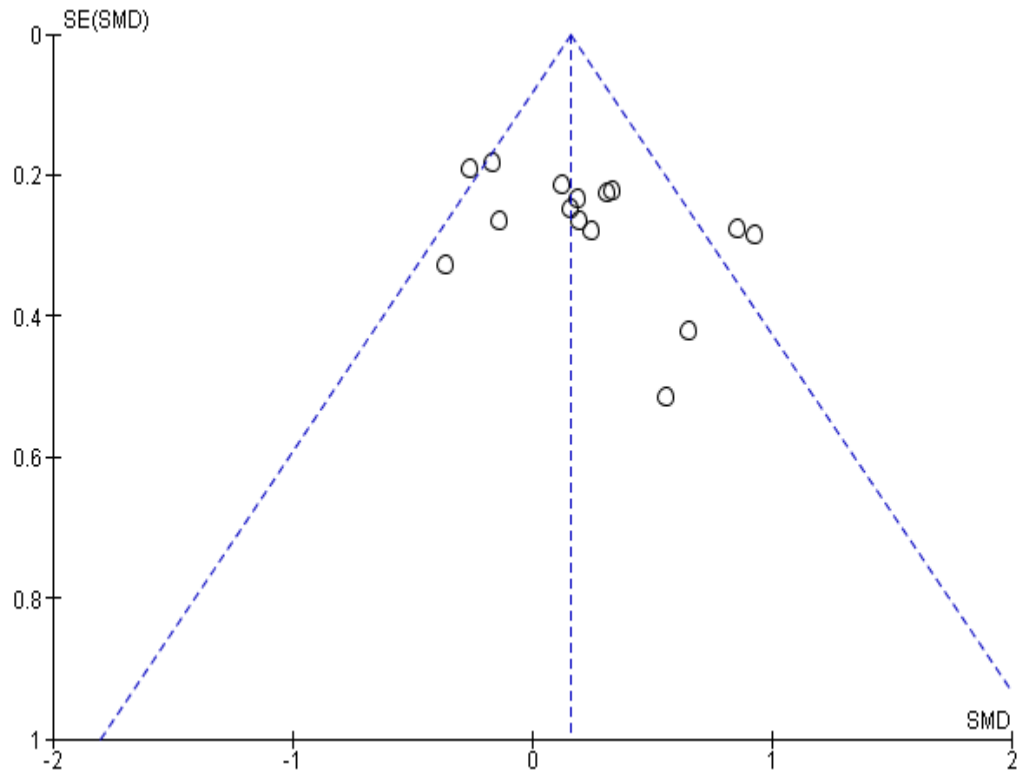
Funnel plot: Upper body strength



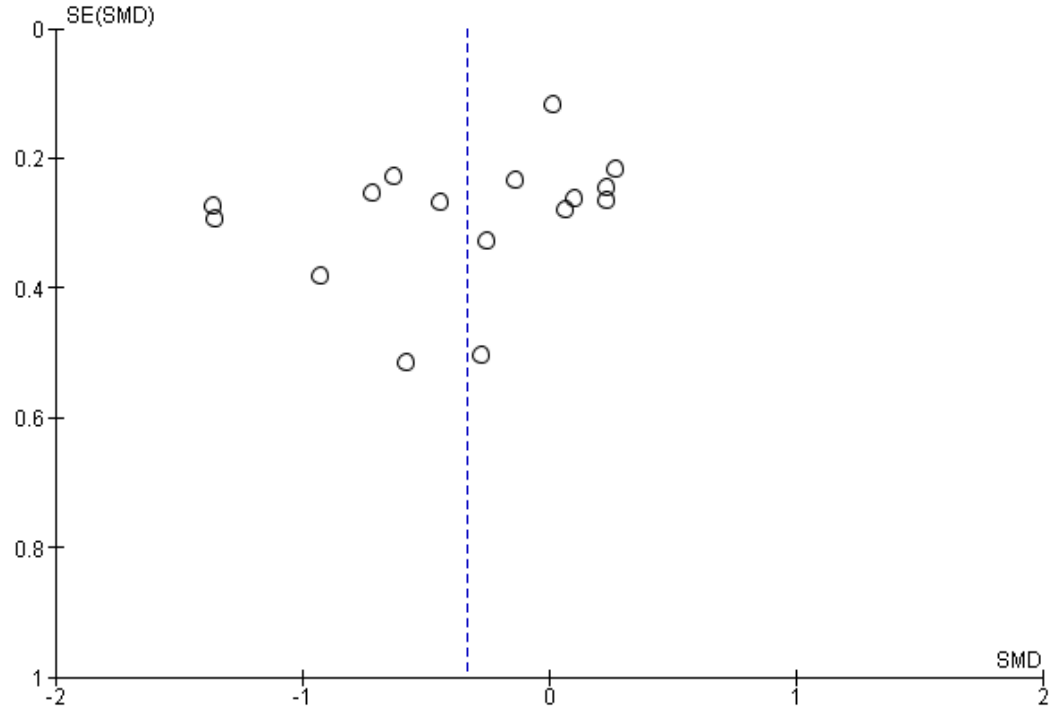
FFunnel Plot: General health-related quality of life



Funnel plot: Physical well-being



Funnel plot: Mental well-being



Funnel plot: Fatigue

Appendix I: Ethics approval documentation (NHS BPS patients)

The Dudley Group of Hospitals NHS
NHS Trust

Russells Hall Hospital
Dudley
West Midlands
DY1 2HQ

RESEARCH & DEVELOPMENT DIRECTORATE
CLINICAL RESEARCH UNIT, 1st FLOOR, NORTH WING
Tel/Fax: 01384 321024/ 01384 456111 Ext 1024

10 June 2009

Mrs Amtul Carmichael
Consultant Surgeon
1st Floor Clinical Offices
Russells Hall Hospital

Dear Amtul

Re: ID780: Levels of awareness and physical activity in women attending National Health Service Breast Screening Programme (PHAST)

I confirm that the Trust is agreeable to the study proceeding according to the approved amended protocol (version 2 dated 11/05/2009).

The Trust has no concerns regarding the potential risks of this study and you will continue to be supported by the Trust in the event of any claim made, as would be the case for any claim made in the normal course of your duties.

The following documents should be used:	
Letter of invitation to participant:	Version 2 dated 20/05/2009
PAR Questionnaire:	Version 1 dated 20/05/2009
PHAST awareness study questionnaire:	Version 1 dated 2008
International Physical Activity Questionnaire:	Long Version revised October 2002
Advertisement:	Version 1 dated 01/12/2008

I wish you and your collaborators well in your investigations.

Yours sincerely

George

Professor George Kitas
Research & Development Director

The Black Country Research Ethics Committee
Osprey House
Albert Street
Redditch
Worcestershire
B97 4DE

Tel: 01527 587599
Fax: 01527 587599

08 June 2009

Mrs Amtul Carmichael
Consultant Surgeon
Russells Hall Hospital, Dudley
Consultant Surgeon
Russels Hall Hospital
Dudley
DY1 2HQ

Dear Mrs Carmichael

Study title:	**Levels of awareness and physical activity in women attending National Health Service Breast Screening Programme**
REC reference:	**09/H1202/10**
Amendment number:	**AMO1**
Amendment date:	**20 May 2009**

The above amendment was reviewed 08 June 2009 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Questionnaire	1	20 May 2009
PHAST information letter	2	11 May 2009
Letter from Brigid Davies		30 April 2009
Notice of Substantial Amendment (non-CTIMPs)		20 May 2009

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

09/H1202/10:	Please quote this number on all correspondence

Yours sincerely

Mrs Brigid Davies
Committee Co-ordinator

E-mail: brigid.davies@westmidlands.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Copy to: Mrs Margaret Marriott, Research and Development Facilitator, Clinical Research Unit, 1st Floor, North Wing, Russells Hall, Pensnett Road, Dudley, DY1 2HQ

The Black Country Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 08 June 2009

Dr Jeff Neilson	Consultant Haematology
Dr J Arunmainayagam	Consultant in HIV & Genitourimary
Rev M Stobert	Lay Member

Appendix J: Ethics approval documentation (Study 3 and 4 RCT breast cancer survivors)

The Dudley Group of Hospitals NHS
NHS Trust
Russells Hall Hospital
Dudley
West Midlands
DY1 2HQ

RESEARCH & DEVELOPMENT DIRECTORATE
CLINICAL RESEARCH UNIT, 1ST FLOOR, NORTH WING
Tel/Fax: 01384 321024/ 01384 456111 Ext 1024

14 July 2009

Mrs Amtul Carmichael
Consultant Breast Surgeon
1st Floor Clinical Offices
Russells Hall Hospital

Dear Amtul

Re: ID800: Physical Activity and Breast Cancer (PHAB) pilot. A feasibility study to increase physical activity in patients with early breast cancer: a pragmatic intervention deliverable and affordable within the NHS.

I confirm that the Trust is agreeable to this study proceeding according to the approved protocol, Version 1 dated 15/05/2009. The Trust has no concerns regarding the potential risks of this study and you will be supported by the Trust in the event of any claim made, as would be the case for any claim made in the normal course of your duties.

The following approved documents should be used:

Letter of invitation to participant:	Version 2 dated 24/06/2009
Participant Information Sheet:	Version 2 dated 24/06/2009
Participant Consent Form:	Version 1 dated 15/05/2009
GP/Consultant Information Sheet:	Version 2 dated 24/06/2009
Flowchart:	Version 2 dated 24/06/2009
Interview Schedules/ Topic Guides:	Version 1 dated 15/05/2009

Enclosed with this letter you will find copies of

(a) the Trust's Policy for taking and documenting informed consent for research studies;
(b) the procedure for reporting serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) in research;
(c) Serious Adverse Events reporting form
(d) the Trust's Policy for addressing fraud and misconduct in research
(e) Chief Investigator's checklist

Please use the reporting form to report any adverse events occurring to patients in your study. Under the Research Governance Framework you are obliged to inform both Dudley Research Ethics Committee and the Trust's R&D Office.

Please also complete and return the Chief Investigator's checklist for this study which forms an integral part of the Trust's research governance policy.

In order to provide documentary evidence that patients have consented to take part in research, the Research & Development Directorate now requires an entry to be made, and a copy of the consent form to be filed in the medical notes of ALL patients participating in research. It is also important to ensure the consent form is completed in its entirety.

NHS
The Black Country Research Ethics Committee
Osprey House
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Worcestershire
B97 4DE

Telephone: 01527 587688
Facsimile: 01527 587501

01 July 2009

Mrs Amtul R Carmichael
Consultant Surgeon
Dudley Group of Hospitals, NHS Foundation Trust, Russells Hall Hospital
Pensnett Road
Dudley
West Midlands
DY1 2HQ

Dear Mrs Carmichael

Full title of study: **Physical Activity and Breast Cancer (PHAB)-Pilot.A feasibility study to increase physical activity in patients with early breast cancer: A pragmatic intervention deliverable and affordable within the NHS**
REC reference number: **09/H1202/81**
Protocol number: **1**

Thank you for your letter of 29 June 2009. I can confirm the REC has received the documents listed below as evidence of compliance with the approval conditions detailed in our letter dated 01 June 2009. Please note these documents are for information only and have not been reviewed by the committee.

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Letter of invitation to participant	2	24 June 2009
GP/Consultant Information Sheets	2	24 June 2009
Participant Information Sheet	2	24 June 2009
Flow chart 1	2	24 June 2009

The Black Country Research Ethics Committee
Osprey House
Albert Street
Redditch
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B97 4DE

Telephone: 01527 587599
Facsimile: 01527 587599

10 June 2009

Mrs Amtul R Carmichael
Consultant Surgeon
Dudley Group of Hospitals, NHS Foundation Trust, Russells Hall Hospital
Pensnett Road
Dudley
West Midlands
DY1 2HQ

Dear Mrs Carmichael

Study Title:	**Physical Activity and Breast Cancer (PHAB)-Pilot.A feasibility study to increase physical activity in patients with early breast cancer: A pragmatic intervention deliverable and affordable within the NHS**
REC reference number:	**09/H1202/81**
Protocol number:	**1**

The Research Ethics Committee reviewed the above application at the meeting held on 01 June 2009. Thank you for attending to discuss the study.

Ethical opinion

The committee said the study was large study and will create a large amount of work.

You said you were hoping the University of Wolverhampton will be able to provide a PhD Student, and you have two surgical trainees providing administrative support for six months while they are looking for a job and yourself.

The committee advised you to change the wording in the Invitation Letter first paragraph second sentence from 'can help' and suggested altering it to it may' .

You agreed to do this.

The committee informed you sending the GP the flow chart may not be particularly useful to them and advised you not to send it to them.

You agreed this was a good idea.

The committee asked you why you were excluding non-English speakers.

You informed the committee that this was a pilot study and do not have access to good advisory systems in many languages and would not be happy if you couldn't deliver at a

level and standard that is appropriate but if you discover physical activity is beneficial non-English speakers would be invited to take part in the Phase III study.

The committee advise you the Patient Information Sheet does not explain what the observational group was and it will need proof reading as there is some repetition and grammatical errors.

You agreed to this.

The committee advised you the flow chart has a word missing in box 'Physical activity not' should have the word 'contraindicated' added after not.

You agreed to correct this.

The Committee advised you that Question A7 in the application has not been ticked.

You agreed to address this.

The committee asked you how you had reached the number of participants.

You informed the committee you had calculated a 30% drop out in your statistics to ensure you achieve useful data to discover the best way to improve physical activity.

The Committee are asking the researcher to;

- Re-submit invitation letter with 'can help' replaced by 'may help'.
- Re-submit Patient Information Sheet explaining who the observational group are, take out any repetition and correcting the grammatical errors.

The members of the Committee present gave a **favourable ethical opinion with conditions** of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Feedback		15 May 2009
Flow Chart	1	15 May 2009
Participant Consent Form	1	15 May 2009
Participant Information Sheet	1	15 May 2009
GP/Consultant Information Sheets	1	15 May 2009
Letter of invitation to participant	1	15 May 2009
Questionnaire: Demographic		15 May 2009
Questionnaire: IRAQ	1	15 May 2009
Questionnaire: QLQ C30	3	
Questionnaire: PAR	1	15 May 2009
Questionnaire: FACT B	1	15 May 2009
Interview Schedules/Topic Guides	1	15 May 2009
Statistician Comments	1	15 May 2009
Covering Letter		15 May 2009
Protocol	1	15 May 2009
Investigator CV		
Application	2.0	15 May 2009

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

There were no declarationsof interests

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

Appendix K: PHAST awareness study demographic information

Name .....

Hospital reference .....

Today's date .....

Date of birth **.....**

Height: **Weight:** **BMI:**
BF%:

Ethnicity:

White – British	☐	Black – other	☐	Asian – other	☐		
White - Irish	☐	Indian	☐	White and black Caribbean	☐		
Other white background	☐	Pakistani	☐	White and black African	☐		
Black – Caribbean	☐	Bangladeshi	☐	Other mixed background	☐		
Black – African	☐	Chinese	☐	Other	☐		

On what date were you diagnosed with Breast cancer? .....

How long ago did you complete your treatment? **.....**

Have you ever been diagnosed with or are you taking treatment for : (Please circle the appropriate answer)

Diabetes	Yes	No
Hypertension (high blood pressure)	Yes	No
High cholesterol	Yes	No

Do you have a first degree relative (parents and brothers and sisters) who have been diagnosed with breast cancer? **(Please circle the appropriate answer)**

Yes No

Do you smoke? **(Please circle the appropriate answer)**

Currently Previously Never

If you do or did smoke, how many cigarettes on average a day, and for how many years?

Number a day: …… Number of years: ……

How many days a week do you drink alcohol?

……

On the days you drink the most how many glasses do you drink?

……

What do you normally drink? (circle the appropriate answer)

Wine **Beer** **Spirits**

Do you have a past history of : (please circle the appropriate answer)

Heart disease (any)	Yes	No
Vascular disease e.g. stroke	Yes	No
Rheumatic fever	Yes	No
Asthma or chronic bronchitis	Yes	No
Gout	Yes	No
Rheumatoid arthritis	Yes	No
Osteoarthritis	Yes	No

Kidney disease	Yes	No
Liver disease	Yes	No

Your marital status (please tick the box closest to your situation)

- ☐ Single
- ☐ Married
- ☐ Living with a partner
- ☐ In a partnership, but not living together
- ☐ Divorced/separated
- ☐ Widowed

How many children do you have? .....

What are were you when you had your first child?……

Did you breastfeed your children? Yes No

Are you menstruating Yes No

If yes,

Are you using a contraception pill Yes No

Are you menstruating regularly Yes No

When did your last period start: …….

Do you or have you ever taken the oral contraceptive pill? Yes

No

If yes how long have/had you taken the oral contraceptive pill (years)? ……

Do you take hormone replacement therapy Yes No

Have you ever taken HRT? Yes No

If yes how long have/had you taken HRT (years)?

……

What is the highest qualification you hold? (tick the box that applies to you)

☐ O-levels or GCSEs

☐ A-levels

☐ NVQ

☐ College degree or diploma

☐ Bachelor's degree

☐ Postgraduate degree or diploma

☐ Other (please give details) .....

How old were you when you left school or full-time education? .....

Occupation now or before retirement (please answer for yourself and your spouse)	**Yourself**	**Your Spouse** .....
Current job status	**Yourself**	**Your Spouse**
Employed full-time	☐	☐
Employed part-time	☐	☐
Homemaker	☐	☐
Student	☐	☐
Unemployed	☐	☐
Unable to work due to illness	☐	☐
Retired	☐	☐

Do you think you do enough physical activity?

No…. ☐ Yes…. ☐ Unsure…. ☐

How do you think the following affect your risk of developing breast cancer?

	Decrease risk	Increase risk	No effect	Don't know
Physical activity	☐	☐	☐	☐
Overweight/obesity	☐	☐	☐	☐

Appendix L: PHAB-PILOT Randomisation Form

Randomisation : ☎ 0800 371 969 or 0800 731 7625 or 🖷 0800 328 6412 (Monday – Friday 9 am to 5 pm)

Caller's Details

Caller's name: Ian Lahart **(please print)**

☎**:** 01384 244015 **Ext:** _____

🖷**:** 01384 244072

Patient's Details

Patient's initials: ☐☐ **(forename & surname)** **Date of birth:** DD / MON / YYYY

Gender: Female ☐ Male ☐

Hospital number: _____ **Investigator:** Mrs Carmichael

Eligibility

All questions must be answered YES for patient to be eligible

	No	Yes
Within 2 years post-diagnosis of invasive breast cancer?	☐	☐
Has the patient given written informed consent?	☐	☐
Date informed consent obtained?	DD / MON / YYYY	
Post-surgery and no surgery planned for the next 6 months	☐	☐
Completed adjuvant therapy	☐	☐
Willing to be randomised	☐	☐
Unable to participate in physical activity because of severe disability (e.g., severe arthritic conditions)	☐	☐
Psychiatric illness	☐	☐
Vulnerable population group	☐	☐
Any other patient where physical activity was not approved by their oncologist.	☐	☐

Stratifying Variables

Has chemotherapy been given? No ☐ Yes ☐

Allocation

Randomisation 1

Allocation 1: Control ☐ Intervention ☐

Randomisation 2

Allocation 2: No ☐ Yes ☐

Patient's Trial Number: ☐☐☐

Completed by: _____

Date of randomisation: DD / MON / YYYY

Appendix M: Patient Information Sheet

PHAB-Pilot

Physical activity and Breast cancer-pilot study

You are being invited to take part in a research project. But before you decide whether you would like to take part it is important for you to understand why the research is being conducted and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP, if you wish.

Ask us if there is anything that is not clear or if you would like more information. Please take your time to decide whether you wish to take part.

In order to make sure that you have some general information about this study we have compiled a list of questions and answers. We hope that this will allow you to make an informed decision as to whether you would like to become involved in this project.

Q: What is the purpose of this study?

A: There are some studies, which show that women who take regular exercise after the treatment of breast cancer may do better and live longer compared to those who are not involved in regular physical activity. Recovering from breast cancer can be a difficult experience both physically and psychologically for many women and they may not feel like doing much exercise. For these reasons, we would like to carry out research to see if we can change the behaviour of women from inactive to active after they have been treated for breast cancer. This research projects will also consider whether exercise can help to improve the general health and well-being of women who have had breast cancer. We hope that this study will provide health professionals with information regarding the benefits of exercise in women who have been treated for breast cancer. This study would last 6 months.

Q: Why have I been chosen?

A: In order to take part in this study you must have completed some form of breast cancer treatment within last 2 months and no longer undergoing active treatment. Women who fulfil these criteria are being invited to participate in this project.

Q: Do I have to take part?

A: No. You are under no obligation to take part in this study. It is up to you to decide whether to take part. If you do decide to take part, you will be given this information sheet to keep and we will ask you to sign a consent form. If you decide to take part in this study and changed your mind afterwards, you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive from the Dudley Group of Hospitals or any other health professional.

Q: What will be involved if I agree to take part in the study?

A. Once the consent form has been signed you will be asked to complete questionnaires to assess the amount of physical activity you do. If the results of the questionnaire show that you already do a lot of physical activity, we will allocate you into the observational group. The details about the observational group are given on page 4 paragraph 1. If the result of the questionnaire shows that you do some physical activity then you will be allocated to take part in one of 2 groups. The requirements of each of these groups are outlined below. It is important to understand that you will be allocated to one of the 2 groups randomly, as if decided by the toss of a coin. We have to do this in order to make sure the results that we get from this are reliable.

Over the course of the study, we would ask you to (irrespective of the group that you are in), to complete a series of assessments at the beginning and at the end (after 6 months) of the trial.

In detail these assessments are:

a) questionnaires that evaluate your levels of physical activity (20 minutes to complete them)
b) body fat and muscle that we measure with an apparatus identical to scales that measure body weight (30 second to complete)

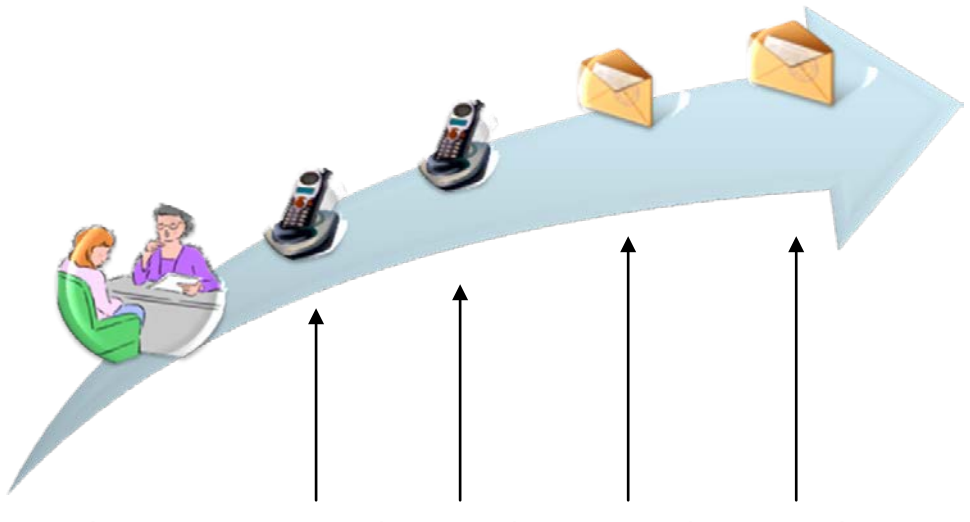
c) We will need a blood sample from you

In addition, some of you will be invited to perform an exercise tolerance test, which is the gold standard (the best possible way of) measuring your fitness (the actual test takes only 8-12 minutes to complete).

Group 1: PHAB-intervention group

If you are randomly allocated to this group, you will be given support and encouragement to do regular exercise. You will be offered a face to face consultation for 30 minutes, 2 telephonic consultations for 15 minutes each and 2 reminders by post to become physically active (Figure 1). We will ask you to build up to regular physical activity equalling to brisk walking for 30 minutes for 5 days a week. All these sessions will be on a 'one-to-one' basis with a trained specialist/researcher. An important feature of the contact session will be exercise counselling; the specialist will encourage you to discuss your thoughts and feelings about exercise and other aspects of your lifestyle. We would also ask you to give a blood sample for the purpose of this research. Finally, some of you will be asked to take a test to check your cardio-respiratory fitness. Both the blood sample and the exercise test will have to be performed at the beginning and at the end of this trial (6 months). If for any reason you feel that you are not able to exercise, you should inform the exercise specialist.

Figure 1.



Group 2: Standard care Group

If you are allocated to this group, you will not receive regular encouragement to exercise. You will complete the questionnaire about physical activity and quality of life at the beginning and at 6 months into the study. We would also like to take from you a blood sample. Finally, you may be asked to take a test to check your cardio-respiratory fitness at the beginning and one at the end of the study at 6 months. Throughout the course of the study, you should continue to live your life as normal.

Q: What are the side effects?

A: Sometimes when people have not exercised for a long time they can experience shortness of breath during exercise and muscle soreness after exercise. During the exercise you may experience fatigue, which stop immediately after you finish with your exercise testing.

Q: What are the possible benefits of taking part?

A: If you are assigned to the physical activity group**,** you will be able to take part in regular exercise, which is known to have benefits for general fitness. If you are assigned to the control group, we will give you advice about exercise at the end of your involvement in the project, if you wish.

Q: Can I withdraw from the study at any time?

A: Yes you can. You are free to refuse to join the study and may withdraw at any time or choose not to answer certain questions. You will receive the same quality of care from the hospital whether you join the project or not. If you think you might be pregnant, you should inform the exercise researcher.

Q: When and where will the project take place?

A: The physical activity recommended is brisk walking for 30 minutes for 5 days a week, any time of the day that is suitable to you. We encourage you to do this exercise in and around your home to minimise inconvenience.

Q: What other information will be collected in the study?

A: With your agreement, we may wish to obtain additional information about the type of treatment you received at the Dudley Group of Hospitals, and your hospital admissions from your medical records.

Q: Will there be any effects on my follow-up screening?

A: No, your participation in the study is not connected to your follow-ups.

Q: What happens when the research stops?

A: Once you have completed the physical activity training, you will be given advice about how to exercise safely on your own. You may choose to join your local gym or exercise club. The exercise specialist will give you help regarding this issue nearer the time.

Q: Will the information obtained in the study be confidential?

A: Anything you say will be treated in confidence. Your name will not be mentioned in any reports of the study and care will be taken so that you cannot be identified from details in reports.

Q: Will anyone else be told about my participation in the project?

A: With your agreement, we will inform your family doctor that you are helping with this study.

Q: What will happen to the results of the research project?

A: We hope to publish the findings from this research project in health science research journals. We will also present the results to Medical conferences and seminars. Only individuals who are directly related to this project will have access to the research data. All data will be kept in a locked cupboard.

Q: Who is organising and funding the research?

A: The study is been conducted by the Breast Unit, Russells Hall Hospital by a team led by Mrs AR Carmichael, Consultant Breast Surgeon.

Q: Who has reviewed the study?

A: Consultants, doctors, exercise physiologists and psychologists. Also, the study is approved from the Research Ethics Committee of our Hospital.

Q: Where can I get some independent information about medical research?

A: You can also get some independent information about Medical Research from a leaflet published by the UK Clinical Research Collaboration. The leaflet is entitled "Clinical trials: What they are and what they're not". This leaflet gives more information about medical research and considers some of the questions you may want to ask. A copy can be obtained from UK Clinical Research Collaboration, 20 Park Crescent, London W1B 1AL.

Q: What if I wish to complain about the way in which this study has been conducted?

A: If you have any cause to complain about any aspect of the way in which you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you and are not compromised in any way because you have taken part in a research study.

If you have any complaints or concerns please contact either the project co-ordinator

Mrs AR Carmichael, Consultant Surgeon, Russells Hall Hospital Dudley; Tel: 01384 244015

OR

Otherwise you can use the normal hospital complaints procedure and contact the following person:

Maria Smith, Business Support Manager, Complaints & Claims Department, Russells Hall Hospital; Tel: 01384 456111 Ext 3548

Thank you for taking the time to consider your participation in this study.

Mrs AR Carmichael, Consultant Breast Surgeon

Appendix N: Informed Consent Form

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: PHAB-Pilot Physical activity and Breast cancer; a pilot study

1. I confirm that I have read and understand the information sheet. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by responsible individuals from the Russells Hall Hospital, University of Birmingham, University of Wolverhampton and from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
4. I agree to my GP being informed of my participation in the study

5. I agree to take part in the above study.

_____	_____	_____
Name of Patient	Date	Signature

_____	_____	_____
Name of Person taking consent	Date	Signature

Appendix O: Demographic information questionnaire

PHAB DEMOGRAPHIC INFORMATION

Name .....

Hospital reference .....

Today's date .....

Date of birth .....

Height: **Weight:** **BMI:**
BF%:

Ethnicity:

White – British	☐	Black – other	☐	Asian – other	☐
White - Irish	☐	Indian	☐	White and black Caribbean	☐
Other white background	☐	Pakistani	☐	White and black African	☐
Black – Caribbean	☐	Bangladeshi	☐	Other mixed background	☐
Black – African	☐	Chinese	☐	Other	☐

On what date were you diagnosed with Breast cancer? .....

How long ago did you complete your treatment? .....

Have you ever been diagnosed with or are you taking treatment for : (Please circle the appropriate answer)

Diabetes	Yes	No
Hypertension (high blood pressure)	Yes	No
High cholesterol	Yes	No

Do you have a first degree relative (parents and brothers and sisters) who have been diagnosed with breast cancer? (Please circle the appropriate answer)

Yes No

Do you smoke? (Please circle the appropriate answer)

Currently Previously Never

If you do or did smoke, how many cigarettes on average a day, and for how many years?

Number a day: ……. Number of years: …….

How many days a week do you drink alcohol? ……

On the days you drink the most how many glasses do you drink? ……..

What do you normally drink? (circle the appropriate answer)

Wine **Beer**

Spirits

Do you have a past history of : (please circle the appropriate answer)

Heart disease (any)	Yes	No
Vascular disease e.g. stroke	Yes	No
Rheumatic fever	Yes	No
Asthma or chronic bronchitis	Yes	No
Gout	Yes	No

Rheumatoid arthritis	Yes	No
Osteoarthritis	Yes	No
Kidney disease	Yes	No
Liver disease	Yes	No

Your marital status (please tick the box closest to your situation)

- ☐ Single
- ☐ Married
- ☐ Living with a partner
- ☐ In a partnership, but not living together
- ☐ Divorced/separated
- ☐ Widowed

How many children do you have?.....

What age were you when you had your first child?

……..

Did you breastfeed your children?.....

Yes ..... No

Are you menstruating	Yes	No
If yes,		
Are you using a contraception pill	Yes	No
Are you menstruating regularly	Yes	No
When did your last period start: …….		

Do you or have you ever taken the oral contraceptive pill? Yes

No

If yes how long have/had you taken the oral contraceptive pill (years)? ……..

Do you take hormone replacement therapy	Yes	No

Have you ever taken HRT? Yes No

If yes how long have/had you taken HRT (years)?

……

What is the highest qualification you hold? (tick the box that applies to you)

- ☐ O-levels or GCSEs
- ☐ A-levels
- ☐ NVQ
- ☐ College degree or diploma
- ☐ Bachelor's degree
- ☐ Postgraduate degree or diploma
- ☐ Other (please give details) .....

How old were you when you left school or full-time education?

……

Occupation now or before retirement (please answer for yourself and your spouse)	**Yourself**	**Your Spouse** .....

Current job status	Yourself	Your Spouse
Employed full-time	☐	☐
Employed part-time	☐	☐
Homemaker	☐	☐
Student	☐	☐
Unemployed	☐	☐
Unable to work due to illness	☐	☐
Retired	☐	☐

Appendix P: International Physical Activity Questionnaire

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (October 2002)

LONG LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation

Translation from English is encouraged to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ

International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective.* Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

   ☐ Yes

   ☐ No → ***Skip to PART 2: TRANSPORTATION***

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

   _____ **days per week**

   ☐ No vigorous job-related physical activity → ***Skip to question 4***

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

   _____ **hours per day**
   _____ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

   _____ **days per week**

   ☐ No moderate job-related physical activity → ***Skip to question 6***

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ **hours per day**
_____ **minutes per day**

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ **days per week**

☐ No job-related walking → ***Skip to PART 2:***

TRANSPORTATION

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ **hours per day**
_____ **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

_____ **days per week**

☐ No traveling in a motor vehicle → ***Skip to question 10***

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ **hours per day**
_____ **minutes per day**

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No bicycling from place to place → ***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ **hours per day**
_____ **minutes per day**

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No walking from place to place → ***Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY***

13. How much time did you usually spend on one of those days **walking** from place to place?

_____ **hours per day**
_____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ **days per week**

☐ No vigorous activity in garden or yard → ***Skip to question***

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ **days per week**

☐ No moderate activity in garden or yard → ***Skip to question 18***

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ **days per week**

☐ No moderate activity inside home → ***Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY***

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ **hours per day**
_____ **minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ **days per week**

☐ No walking in leisure time → ***Skip to question 22***

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day**
_____ **minutes per day**

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ **days per week**

☐ No vigorous activity in leisure time → ***Skip to question 24***

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day**
_____ **minutes per day**

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ **days per week**

☐ No moderate activity in leisure time → ***Skip to PART 5: TIME SPENT SITTING***

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?
_____ **hours per day**
_____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ **hours per day**
_____ **minutes per day**

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

_____ **hours per day**
_____ **minutes per day**

This is the end of the questionnaire, thank you for participating.

Appendix Q: FACT-B (Version 4)

English (Universal) 16 November 2007

This a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

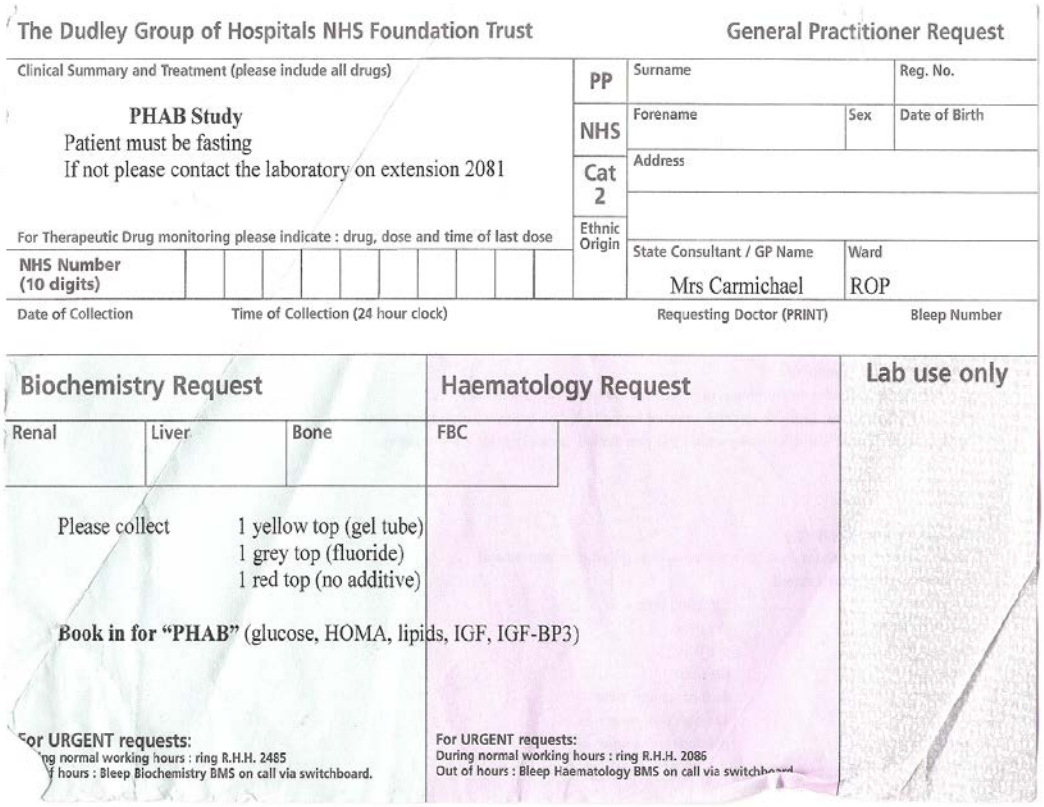
Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

Appendix R: Blood form for biochemistry request



The Dudley Group of Hospitals NHS Foundation Trust

General Practitioner Request

Clinical Summary and Treatment (please include all drugs)

PHAB Study
Patient must be fasting
If not please contact the laboratory on extension 2081

For Therapeutic Drug monitoring please indicate : drug, dose and time of last dose

PP | NHS | Cat 2 | Ethnic Origin

Surname | Reg. No.
Forename | Sex | Date of Birth
Address
State Consultant / GP Name: Mrs Carmichael | Ward: ROP

NHS Number (10 digits)

Date of Collection | Time of Collection (24 hour clock) | Requesting Doctor (PRINT) | Bleep Number

Biochemistry Request

Renal | Liver | Bone

Please collect
1 yellow top (gel tube)
1 grey top (fluoride)
1 red top (no additive)

Book in for "PHAB" (glucose, HOMA, lipids, IGF, IGF-BP3)

For URGENT requests:
ng normal working hours : ring R.H.H. 2485
f hours : Bleep Biochemistry BMS on call via switchboard.

Haematology Request

FBC

For URGENT requests:
During normal working hours : ring R.H.H. 2086
Out of hours : Bleep Haematology BMS on call via switchboard

Lab use only

Appendix S: Physical activity: Script for face to face and telephonic consultation

Please emphasise moderate intensity physical activity message

Current PA Behaviour

- Activities the patients enjoyed & felt they could do on a regular basis ☐
- Ways of fitting PA into daily life; previous experiences ☐

Decision Balance Sheet

- Possible gains and losses that might occur with increased activity leve ☐

Perceived Barriers

What are the greatest barriers and how they might be overcome? ☐

Suggest exercise benefits patients may not be aware of ☐

Prompts to seek social support

- Family, friends, workmates, others who might encourage exercise ☐
- Someone to talk to while exercise & to provide encouragement ☐

Goal setting ☐

- Patients states own goals
- Please help determine short term goals. ☐

Safety advice

- Walking/cycling in dark, ensure can be seen and someone knows ☐
- Where you're going. Avoid busy/dangerous roads etc. ☐

Go for brisk walk

- Brisk walk so that you are mildly breathless but can still hold a conversation ☐

Basic lifestyle information

- Dietary info, portion size, fat, smoking, hydration – generally and during activity ☐

Appendix T: Post card physical activity prompt

I HOPE YOU HAVE BEEN KEEPING PHYSICALLY ACTIVE!

Benefits:

- Combat stress & anxiety
- Relax & sleep well
- Improve quality of life
- Increase your stamina
- Maintain a healthy weight

Why not try.....

- Using the stairs instead of the lift
- Walking to the shops or work instead of driving
- Do exercise you enjoy
- Fit some form of activity into your daily routine

Through exercise you have a powerful tool for improving your health

PHAB-pilot 15/5/9